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DISEASE OF THE CORONARY ARTERIES WITH A CONSIDERATION OF DATA ON THE INCREASING MORTALITY OF HEART DISEASE.*

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Different diseases occupy the center of the stage at different times. In my early days in medicine typhoid fever was of paramount interest. Its conquest achieved in the course of a few years—one of the greatest triumphs of medicine—brought another disease into the limelight, namely, tuberculosis. Tuberculosis has now fallen low among the causes of death and bids fair within the lives of persons now living to join the list of deceased diseases. Pneumonia, never far removed from the center of the stage, has not greatly changed its position in the last half century. For the aged it is still the Captain of the Men of Death, but in youth and middle life it is perhaps less of a menace now than formerly. What occupies the center of the stage to-day? Undoubtedly heart disease.

Everywhere heart disease has leaped to the top of the list of causes of death and this is only in part due to the lowered mortality from other diseases. The actual increase in deaths from heart disease, however, in reality represents a triumph of preventive medicine. Young adults are escaping the ravages of tuberculosis and of occupational diseases. More are now living to the age period beyond

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40 when heart disease, vascular degeneration and cancer prevail. By the prolongation of the average span of life, to 59 years as it now is, more individuals are kept alive to die in the higher age groups from those diseases that afflict advancing years. It should be mentioned that C. F. and N. W. Bolduan[1] seek to show that the "appalling increase" in heart disease is fictitious. The registered increase in heart disease is, they believe, merely due to a change in terms used in death certificates, such conditions as apoplexy, Bright's disease and senility frequently being listed as heart disease. I cannot feel that this is the correct, certainly not the complete explanation. The tables I have gathered from various sources* are so concordant that one must conclude there is an actual and not merely a relative increase of deaths from heart disease (Table 1).

TABLE 1.—INCREASING MORTALITY FROM HEART DISEASE (HEALTH DEPARTMENT OF NEW JERSEY).

(Rates per 100,000 Population.)

Age periods.	1922.	1932.
30 to 39	8	10
40 to 49	13	19
50 to 59	24	38
60 to 69	39	56
70 to 79	41	62
80 to 89	21	30
90 and over	2	5

It should be borne in mind in considering these figures that the rates are based upon total population and that the percentage of the population in the given age groups for 1932 may vary considerably from the percentages for 1922.

TABLE 2.—INCREASING DEATHS FROM HEART DISEASE IN CERTAIN AGE GROUPS IN DETROIT.

(Rates per 100,000 Population.)

Age groups.	1923.		1932.	
	No.	Rate.	No.	Rate.
Under 5	22	18.7	13	9.3
5 to 9	21	22.5	11	7.8
10 to 14	31	42.8	21	16.5
15 to 19	26	34.9	24	20.5
20 to 24	46	39.8	28	19.4
25 to 29	51	36.8	48	29.6
30 and over	1374	314.0	2416	364.0

The Detroit statistics show the same thing. They demonstrate a tremendous falling off in deaths from heart disease in the early years of life up to 29. After 30, however, there is a much heavier toll now than a decade ago—364 per 100,000 as against 314 (Table 2).

* Dr. Dublin, of the Metropolitan Life Insurance Company, Dr. Lehrfeld, of the Department of Health of Philadelphia, and Dr. Mahaffey, of the Health Department of New Jersey, have kindly furnished us valuable data.

The following table gives the relevant statistics for Philadelphia:

TABLE 3.—PHILADELPHIA DEATHS FROM HEART DISEASE—1923 TO 1932.

Year.	Total deaths	Rate per 100,000 population.	Under 10 yrs.	10 to 20 yrs.	20 to 30 yrs.	30 to 40 yrs.	40 to 50 yrs.	50 to 60 yrs.	60 to 70 yrs.	70 to 80 yrs.	80 to 90 yrs.	90 to 100 yrs.	100 and over
1923	4580	245.3	79	116	134	269	464	819	1122	1028	480	66	3
1924	4349	231.4	77	134	143	218	448	788	1035	996	455	53	2
1925	5097	269.4	53	135	184	288	531	898	1242	1143	544	78	1
1926	2937	311.7	55	101	182	291	648	1027	1566	1387	586	89	5
1927	4762	248.4	56	106	139	279	508	844	1214	1098	446	69	3
1928	4394	227.7	56	80	120	258	485	809	1113	975	451	46	1
1929	4418	227.5	63	103	148	230	441	823	1089	1019	433	68	1
1930	4454	228.0	40	75	132	223	452	806	1132	1091	443	59	1
1931	4363	221.9	33	50	118	208	420	786	1106	1096	484	59	3
1932	5709	288.5	30	91	125	266	528	1019	1594	1339	631	86	

I do not know how to explain the uniformly high figures after 40 for the year 1926, unless one attributes it to the prevalence of acute respiratory infections during that year, since statistics show that such infections influence the death rate from other diseases unfavorably. Very striking is the increase of 1932 over 1931. In England and Wales there seems also to be a steady increase in deaths from heart disease since 1921, but with an encouraging decline in 1931 and 1932.

To sum up: Whether there is or there is not an "alarming increase" in deaths from heart disease, the fact is that heart disease stands at the head of the list. This makes it a definite problem in health conservation in the sense that efforts should be made to postpone as late as possible death from those degenerative diseases among which that of the heart and bloodvessels is the most important. Degeneration is the price of old age and mankind prefers to pay that price as late as possible. From a detached biologic point of view this may not be a desirable aim—an old tree bearing no fruit or only a few green leaves had better give place to a younger one—but society today with its humane instincts seeks to keep alive the cripple as well as the lean and slippered pantaloon.

I shall not go into the history of coronary occlusion. Nearly everyone who writes exhaustively on the subject finds as he proceeds an earlier reference than his literary predecessors. I believe, however, that I have discovered the earliest recorded case—and yet some future writer may find an earlier one. In Homer's Odyssey,[2] it is stated that Phoebus Apollo shed down his gentle darts upon Phrontis, son of Onetor, Menelaus' navigator, and "he dropped dead with the steering oar of the moving ship within his hands." This impresses me as an instantaneous painless coronary death.

No one in recent years has contributed more to our understanding of the subject of coronary disease than J. B. Herrick of Chicago. Credit also belongs to George Dock, E. R. LeCount and many others. The first case of coronary thrombosis diagnosed during life as far as I have been able to ascertain, was reported by Hammer[3] who had observed it in 1876. It was confirmed at autopsy although the pathologic description is not very clear. Hammer incidentally cites a sentence from Cohnheim written in 1877 which shows the fallacy of prophecy. "It is a fact that Bezold through experimental closure of a coronary artery was able to bring the heart to a stop. Whether, however, a similar phenomenon will ever be observed in human pathology seems to me very improbable."*

Not much space need be given to a consideration of the causes for the simple reason that we know so little about them. We can say under what conditions coronary disease may occur but that is far removed from explaining its etiology. Coronary disease, particularly coronary thrombosis, prefers the male sex between the ages of 50 and 70, although it may occur much earlier. Smith and Bartels[4] report 2 cases and collect 20 from the literature of ages from 12 to 40. Coronary occlusion is more common in private than in charity hospital practice, indicating that social status is a factor. High blood pressure is an important element, but typical cases occur also in persons with low blood pressure. Syphilis, strange to say, is not a significant factor either in my personal experience or in the literature. It is important only when it produces atresia of the coronary ostia by extension from the aorta. Diabetes is by many considered an important factor (Nathanson[5]), although in my own series it does not appear to play a conspicuous rôle. Nephritis, thromboangiitis obliterans and polycythemia rubra play their part. An embolus derived from a mural thrombus or rarely from a diseased valve may also cause occlusion.

That polycythemia through inspissation of the blood might favor coronary thrombosis is theoretically possible and has been demonstrated in 1 of my cases. (See also Boyd.[6])

That infectious diseases in earlier life may play a rôle is a possibility that needs further investigation.

Heredity was an apparent factor in 27 per cent of my own cases of coronary disease. But in what heredity consists, whether it merely predisposes, the environment doing the rest, or whether it carries on through generations the actual elements of the disease, we do not know. Heredity and the closely related constitution are subjects in which as far as any real knowledge is concerned we are still, to use Dean Brown's phrase, in the Desert of Moab. Habits, such as a too sedentary or too athletic mode of life, are also possible agents but as they are far more widely prevalent than is coronary disease,

* Those interested in the history of coronary disease will find a fairly complete account in Warburg's articles (Acta med. Scand., 1930, **73**, 425).

some additional factors must be operative and that X factor is perhaps the inherited constitution. Whether that is something chemical or something anatomic remains to be discovered.

Regarding habits, I believe that worry is one of the most effective in producing the coronary syndrome; overeating, overindulgence in sexual relations, especially if these are not accompanied by complete gratification, overambitiousness, also are prominent in the histories of coronary cases if we but search for them. The alcoholic habit of itself, if not a by-product of the others mentioned, does not seem to me to lead to coronary disease. I cannot give the same clean bill of health to tobacco. One-fourth of the patients with coronary occlusion that I have seen were heavy smokers. Here again it must be admitted that not all who smoke to excess become victims of coronary disease but the number that do is sufficiently large to make me rank tobacco definitely among the causes.*

Acute coronary closure may be precipitated by any unusual physical effort, by emotional excitement,† during coitus, during public speaking, through fatigue after an arduous journey or from play, or by any trying experience.‡ Sometimes, however, no immediate exciting cause is discoverable. When the attack occurs during sleep I have thought it possible that a harrowing nightmare was the *agent provocateur*. MacWilliams has shown that the blood pressure may rise 20 to 30 mm. during dreams or uneasy sleep.

There is no physical or bodily habitus characteristic of patients destined to have coronary disease. Perhaps the stocky, short-necked, overweight, hypertensive individual predominates but the slender and spare are not exempt. Many have tortuous temporal arteries and arcus or annulus senilis. The radial arteries may be soft but in many instances they are thick and leathery, rarely beaded.§ The majority of "coronary" individuals are active and athletic, often passionate golf players, but the disease as I have said occurs among the sedentary as well. The greater proportion are heavy eaters. Many are given to liberal night suppers, and the excessive use of tobacco is a common habit.

As coronary anastomoses are said to be richer in persons of advanced age, it is not surprising that individuals over 70 rarely die of coronary occlusion (Barnes[9]).

* The work of Sulzberger and Harkavy[7] shows that many persons have tobacco sensitiveness. Harkavy found 13 patients among 36 suffering from coronary artery disease sensitive to tobacco by skin tests. The average age of the patients who reacted to tobacco was 45 years; the average age of coronary patients who failed to react to tobacco was 60 years.

† As John Hunter said over a century and a half ago—"My life is in the hands of any rascal that chooses to plague me."

‡ Fitzhugh and Hamilton[8] believe that drugs, such as thyroid extract, may bring on an attack; insulin and adrenalin may also do so.

§ It should be borne in mind that soft radials are no proof that the arterioles of the heart or of the brain are normal—they may be in a state of advanced sclerosis.

Symptomatology. The symptoms of acute sudden closure of a coronary artery of considerable size are dramatic in the extreme. The patient, usually a man past 50, florid, thick-necked and heavy-set, is seized suddenly with an unendurable pain, in its fearful severity unlike anything he has ever experienced before. His face becomes ashen or bluish-gray, exsanguined and pinched. A cold sweat breaks out over his body, the extremities become cold, the pulse small and thready, and usually rapid although sometimes it is slow. In certain cases no pulse is obtainable. The patient is apprehensive to the highest degree; he is sure death is in the offing. He may lose consciousness and may have a convulsion. The heart sounds are feeble, the first sound at the apex scarcely audible; frequently a systolic murmur not heard before is found at the mitral area or over the body of the heart. Respiration is shallow and restricted; there may be shortness of breath and air hunger; sometimes the breathing is of the Cheyne-Stokes type. Râles may be heard over the bases of the lungs: sometimes pulmonary infarction occurs with spitting of blood. The blood pressure usually drops precipitously, sometimes to a point when none is obtainable by the auscultatory method. I have seen it fall from 220 systolic to 90 in the course of a few hours in a patient who nevertheless recovered.

The pain is of a crushing, crunching or tearing character and is situated usually behind the middle or lower sternum, or in the region of the parasternal lines on both sides of the chest, or in the epigastrium, or even in the umbilical region. It is, as a rule, stationary, but it may radiate into one or both arms, to the lower cervical region in the back or up into the jaws. In several of my cases the pain in the left elbow was more severe than the substernal pain.

The attack may be accompanied by vomiting and marked abdominal distention, so that it closely resembles an acute abdominal catastrophe such as perforation of a peptic ulcer, biliary colic, acute pancreatitis, mesenteric thrombosis or the gastric crises of tabes.

As the outstanding features are those of shock, the temperature is low in the beginning but it soon starts to rise to 100° F. or higher, rarely above 103°. This is probably a protein fever caused by the absorption of degradation products from the infarction in the heart. To the same cause is to be ascribed the leukocytosis that appears soon after the onset of the thrombosis. Libman has detected it as early as $1\frac{3}{4}$ hours after the commencement of an attack. It usually ranges between 12,000 and 20,000 but may reach as high as 30,000. If the leukocytosis persists or increases in the absence of a complication it is indicative of progressive necrosis of the heart wall which may lead to cardiac rupture or to aneurysm. In some cases, especially if the obstructed artery is the anterior coronary, a small patch of pericardial friction, corresponding in all probability to the area of infarction, can be detected; at times the pericarditis extends far beyond the infarcted area. Enlargement of the liver is indicative,

in the early stages before any congestive heart failure has taken place, of closure of the right coronary artery. In such cases slight jaundice may occur. Albuminuria is usually present and in rare cases sugar has been found in the urine.

I have said that the patient is panic stricken by fear of death yet I have seen individuals who although convinced of the close approach of death, were never emotionally or psychically paralyzed with fear. They realized that their time had come but were unafraid.

While the picture I have sketched is perhaps the most common, it is not the invariable one. Coronary occlusion may cause instant death without any preliminary pain. Such apparently painless deaths are not uncommon on the golf links and in other public places. Sometimes if the patient has had a little bloating and belching of gas before, the death is attributed, at least in the newspapers, to acute indigestion. It is of course impossible when confronted with an instantaneous death to be sure before the autopsy of what has actually taken place—whether there is a coronary obstruction or whether death was due to angina pectoris without obstruction.* This goes to show how closely the two conditions, coronary thrombosis and angina pectoris, are allied. What is commonly called "status anginosus" is most often a progressive coronary occlusion and not simply cumulative attacks of angina pectoris. In the acutely fatal cases there is no time, even if a thrombus is present, for infarction to form.

In some cases after a 24- or 36-hour period of profound collapse during which life seems to hang by a thread, the patient being perhaps in a stupor, there is a sudden improvement in the symptoms, giving rise to the hope that all danger is passed. Such hope, however, is often illusory. The patient while talking or eating may suddenly drop back dead. If one is watchful one can detect in this type of case during the interval of improvement definite signs of grave myocardial damage.

Psychic disturbances are not rare in the severer types of coronary occlusion. They may take the form of confusional and hallucinatory states, of delusions, of acute maniacal outbursts and of attacks resembling delirium tremens. In every surviving case that I have seen the psychosis disappeared completely.

Larval Coronary Disease. In addition to acute coronary closure there is a form of coronary disease that does not present a sufficiently striking picture always to be recognized. Anatomically it consists of a gradual narrowing of the coronary vessels due to a progressive endarteritis. The result is a lessening of the blood supply with a consequent oxygen deprivation of the tissues, a condition I have called histanoxia. This histanoxia may lead to degenerative changes in the muscle fibers and their replacement by fibrous

* Sudden death has, of course, many other possible causes—apoplexy, rupture of aneurysm, etc.

tissue. Clinically it may manifest itself in various ways. One is the usual type of chronic congestive heart failure. The other is more specifically coronary and presents the following symptoms:

There may be a sense of substernal oppression which, as a rule, is relieved by rest. As belching is not infrequent, patients as well as physicians often interpret such seizures as due to indigestion, an error from which there is a sad awakening, not for the patient, but for the doctor. Attacks of fainting may also be produced by this type of chronic coronary artery disease. And then there are sudden mild attacks of heart failure approaching fainting, with pallor, sweating and great restlessness, but with absence of pain.

Any of the mild forms may without interruption pass into a grave form. Thus in the case of Mr. W. (seen with Dr. H. S. Read) the patient experienced a peculiar empty or vacuum feeling, as he called it, in his chest and soon afterward went into collapse with *angor animi*, falling blood pressure and with electrocardiographic findings of coronary occlusion, although he never had any acute pain. He was compelled to remain in bed for 9 weeks.

Acute pulmonary edema with inky cyanosis may be a manifestation of coronary disease. This condition, in its suddenness and violence, often tests the doctor's resourcefulness and intelligence. The best measures for combating it are: Venesection, morphin and atropin, and, if need be, dry cupping over the chest.

The fluoroscope may give evidence of coronary disease in showing feeble contractions, a see-saw type of contraction (Ernstene[10]). It would seem to be unwise, however, in the early stages at least, to subject the patient to the strain of such an examination. Ernstene[10] points out a lessened vital capacity in cases of coronary disease. In several instances I found absence of the dorsalis pedis pulse as collateral evidence of arteriosclerosis; in a few cases there was a history of intermittent claudication.

Electrocardiographic Evidence. *Angina Pectoris.* There are no characteristic changes in the electrocardiograms in patients suffering from angina pectoris during the intervals between paroxysms and in many cases during the attack. In others, however, certain alterations in the ventricular complexes occur. During the paroxysm the *T* waves in Lead I, in Lead II, or in both, may become diphasic or inverted when they are upright between attacks or more deeply inverted if they are already abnormal.* The severity of the pain does not seem to determine whether or not changes in the electrocardiogram will occur, but the degree of change when present is greater during more severe attacks.

Coronary Sclerosis. The electrocardiogram is not necessarily altered in sclerosis of the coronary arteries. Conduction defects,

* These changes are similar to those seen in electrocardiograms of dogs when branches of the coronary arteries are experimentally occluded and support the theory that during attacks of angina the blood supply of the myocardium is deficient.

however, not infrequently occur. Thus the commonest cause of intraventricular block is coronary disease, and various types of arrhythmia, auriculoventricular delayed conduction, low voltage, and splintering of the *Q R S* complexes are sometimes seen.

Coronary Occlusion. In coronary occlusion the electrocardiographic changes vary with the size of the infarcted area and with its position in relation to the plane of the leads employed. The most common site of thrombosis—the descending branch of the left coronary artery, the infarct being near the tip of the left ventricle—gives rise to characteristic changes in the electrocardiogram. Soon after closure of the vessel the *Q R S* complex becomes slurred or decreased or widened and the *T* wave in Lead I takes off high on the downstroke of the *R*, with an initial upward deflection and a terminal depression. Coincidently the *S–T* interval in Lead III is depressed and the *T* wave inverted. Similar though less characteristic changes occur in Lead II. During the succeeding days the *T* wave in Lead I and often in Lead II becomes deeply inverted, with an elevated *S–T* interval, while in Lead III the *S–T* interval remains depressed and the *T* wave becomes upright. In favorable cases the electrocardiogram may return to normal with repair of the infarct, but often some evidence remains in an altered *S–T* interval or *T* wave in Leads I and III.

In cases where the right coronary artery has been occluded the electrocardiogram shows first a high origin and later inversion of the *T* wave in Lead III, and depression of the *S–T* interval in Lead I.

Thrombosis of other branches of the coronary arteries shows no changes or less characteristic alterations when the conventional leads are used. Thus it has been pointed out recently that an abnormal *Q* wave in Lead III in the absence of right axis deviation is often the only electrocardiographic evidence of occlusion. The use of anteroposterior leads as suggested by Wolferth and Wood,[11] the electrodes being placed directly on the chest, or of multiple leads as employed by Hyman, have shown abnormalities of the *S–T* intervals and *T* waves in a number of cases where the infarct was present in an area "silent" to the usual leads.

Differences Between Angina Pectoris and Coronary Thrombosis. Although at times it is difficult to distinguish between these two, since they are closely related pathogenetically, there are certain differences that should be borne in mind from their importance both in diagnosis and in prognosis. While in all probability angina pectoris is a "coronary affair" to use a French phrase, it may occur in persons who give no evidence by any known test of coronary disease. Pathogenetically it differs from coronary thrombosis in that it is due, so we believe, to a transitory spasm of coronary artery and not to a real plugging of the vessel.

The important clinical differences are indicated in the following table:*

TABLE 4.—CLINICAL DIFFERENCES BETWEEN ANGINA PECTORIS AND CORONARY THROMBOSIS.

	Angina pectoris.	Coronary thrombosis.
Beginning of attack	During effort	During rest.
Seat of pain	Behind middle of sternum	Behind lower sternum or in epigastrium.
Radiation	To left shoulder and down left arm	May be absent.
Dyspnea	Not present	Marked.
Behavior of patient	Quiet	May be restless.
Duration of attack	Few minutes	Hours to days.
Shock	Absent	Present.
Vomiting	Rare	Frequent.
Pulse	Unchanged or tense	Small, often rapid.
Arrhythmia	Rare	In about 15 per cent.
Temperature	Normal	Elevated.
Blood pressure	Unchanged or rises	Falls or remains stationary.
Heart sounds	Normal	Frequently soft; pericardial friction often present; at times gallop rhythm.
Congestive signs	Absent	Often present.
Electrocardiogram	Often normal	Usually characteristic.
Nitrites	Useful	No effect.
Leukocytosis	Absent.	Present.

DIFFERENTIAL DIAGNOSIS. *Pericarditis* independent of coronary occlusion is not often painful but it may be. While one would be likely to conclude that an acute painful pericarditis had a thrombotic or embolic infarct as its cause, in young persons and even in the elderly an acute pericarditis of infective or uremic origin may be painful and simulate angina pectoris or coronary occlusion.

Pneumothorax. In 1 case seen in consultation a diagnosis of angina pectoris had been made. When I saw the patient some hours after he had been seized he was still suffering severe chest pain. The man was a builder and the attack had come on while he was at work on a building. Upon examination I found that he had a spontaneous pneumothorax.

In another case *herpes zoster* of the thorax produced a picture that had led to a diagnosis of angina pectoris or rather of coronary thrombosis. There were only a few papules visible at the time I made my examination, but as they began at the spine and were present in the axilla, the correct diagnosis was readily made.

Angina pectoris and coronary occlusion may also be simulated by *myalgia, intercostal neuralgia, nervous dyspepsia,* and *hysteria.* The hysterical mimicry is illustrated by the following case:

A woman, about 52, a very important member of my early clientèle, whose sister was suffering from angina pectoris, began to have similar

* Modified from Warburg (Acta med. Scand., 1930, **73**, 547), Parkinson and Bedford (Lancet, 1928, **1**, 4; Heart, 1928, **14**, 195) and Keefer and Resnik (Arch. Int. Med., 1928, **21**, 769).

attacks of precordial pain radiating into the arms and having a considerable duration. They usually came on after a domestic scene, a frequent occurrence. I took them to be hysterical. One day while conducting a dispensary clinic I received a message to come at once, as Mrs. D. was having a terrible attack and seemed to be dying. My first thought was, "Have I been mistaken in my diagnosis?" The taxicab seemed to crawl at a snail's pace. As I approached the house I fully expected to see the undertaker's wagon at the door. I rushed upstairs and found the patient sitting by the open window moaning with pain and declaring herself convinced that the end was near. Finding her pulse good and no evidence of shock I tested sensation with a pin and found her completely anesthetic for touch and pain up to the elbows. This lady lived for many years and died eventually from a delayed cerebral hemorrhage (Spätapoplexie) after an automobile accident.

Differential Diagnosis from Abdominal Conditions. As I have said coronary occlusion may closely simulate an acute abdominal accident. The following are the more important:

Gall Stone Colic. Although differential diagnosis is sometimes exceedingly difficult, the history of previous substernal oppression, the profound degree of shock, the absence of tenderness in the gall bladder area, the male sex, are useful guides. If fever, leukocytosis and pericardial friction develop the diagnosis can no longer be in doubt. It must, however, be borne in mind that if the right coronary artery is obstructed, there may be a rapid swelling of the liver with tenderness, which might mislead.

In 1 case in which our diagnosis see-sawed between an acute cardiac seizure and a gall stone attack, the patient could only find comfort by getting on all fours. We decided in favor of a cardiac attack but the autopsy revealed a ruptured dissecting aneurysm.

Mesenteric Thrombosis. In 1 case coming under my observation the question of the possibility of mesenteric thrombosis arose.

A man in the early forties, who had a history of pernicious anemia from which he seemed to have recovered except for symptoms of combined spinal sclerosis, was seized with sudden sharp pain in the epigastrium with vomiting, blood in the bowel movements, and marked abdominal distention. At autopsy the man had no definite cardiac infarct but a firm antemortem thrombus in the apex of the left ventricle. There was no thrombosis either of the mesenteric arteries or veins.

Rupture of a peptic ulcer may resemble acute coronary thrombosis. The diagnosis has to be made on a careful history and on a thorough physical examination.

A tabetic crisis may conceivably simulate coronary occlusion. One should always make it a habit in every obscure case of severe epigastric pain to test the ocular and tendon reflexes.

Acute Pancreatitis. I have seen 1 case in which it was very difficult at the moment to tell whether the patient had coronary occlusion or acute pancreatitis. The conclusion was finally reached that the man had had some abdominal catastrophe and at operation acute pancreatitis was found.

Diabetic Acidosis. It is sometimes very difficult to tell whether a severe chest pang in a patient suffering from diabetic acidosis is or is not due to coronary block. As the use of insulin is dangerous in coronary occlusion, the diagnosis has much more than academic interest. It might be well in a doubtful case to treat the patient with alkalies and orange juice. If the symptoms disappear with lessening of the acidosis, then they were in all likelihood not due to coronary thrombosis.

Prognosis is often a more difficult art than diagnosis, and yet the doctor's reputation to a large extent stands or falls by it. In coronary occlusion it is particularly hazardous to venture a prediction as is shown in the 2 following cases:

Mr. H., a Philadelphia merchant, aged 54, who 7 years before had had an attack of angina pectoris, was seized with a violent pain in his chest. He was in Paris at the time. A physician was called who appreciated the gravity of the case and summoned a renowned cardiologist. The latter correctly diagnosed coronary occlusion and in a rather brutal way said to the wife, "Madam, your husband will die." The distracted lady insisted that the family doctor stay all night. The next morning the patient was very much better. The consultant on his second visit was amazed at the man's improvement and turning to the wife said, "Madam, I think I was mistaken. Your husband is going to recover." That night the patient had another violent seizure and died.

The second patient, a man with polycythemia rubra, had a typical coronary attack, with fever and leukocytosis and pericardial friction. Within 2 or 3 days the symptoms had entirely subsided. About a week later, when apparently convalescing, he sat up to eat his lunch and dropped over dead.

It is probable that in both these patients there was a ventricular rupture at the site of the infarction or a sudden ventricular fibrillation.

There are, however, certain features that permit a fairly definite prediction. A persistent tachycardia especially with gallop or other disturbance of rhythm, a continuing fall of blood pressure, unyielding pain, and hyperpyrexia,[12] make the prognosis unfavorable. Great severity of pain is, however, not of necessity a fatal omen. In 1 of my cases morphin utterly failed to control the pain; chloroform held it in check just as long as the patient was under its influence. Nevertheless, the man recovered and lived for a number of years, in fact lived through a second attack and through an attack of pneumonia. A rise in blood pressure is a favorable sign.

. Patients that have shown symptoms of coronary disease either of the mild or of the painful type are not good subjects for operation. The mental strain may produce angiospastic disturbance in the coronary circulation and may precipitate an attack, the patient dying on the table or shortly afterward. Hence all operations of election should be avoided.

The earlier we can see these patients the better, but whenever we see them we must recognize the true condition and not be misled

by the prominence of gastric symptoms. It is in the early stages that much can be done and the catastrophe of sudden occlusion either obviated or postponed to a late period when life no longer is very important. In any patient passed 50 an unaccustomed, uncomfortable feeling behind the sternum coming on during walking or on any physical effort should awaken a suspicion of some cardiac abnormality. True, nothing may be discovered on physical examination, though there is often a slight enlargement to the left, a snappy second aortic sound or a systolic murmur at the aortic area. An elevated blood pressure helps in directing the medical mind in the proper channel. The electrocardiogram may show some abnormality, a change in the *Q* or in the *T* wave. But the experienced and careful clinician does not need that; he reads the writing in the patient.

Treatment divides itself into two parts, treatment of the attack and subsequent treatment. That of the attack is more or less stereotyped and presents perhaps but one controversial feature and that is the use of digitalis. I shall refer to this in a moment. The following is an epitome of the treatment of the attack.

Absolute rest, mental and physical, the most absolute conceivable. It may be inadvisable to undress the patient at the outset. He should have no company and should not be allowed to talk. He should of course use the bed pan and urinal and should have a night and a day nurse when the circumstances permit. External heat should be applied.

For the relief of pain nothing compares with morphin in large doses. When morphine fails hardly anything else is likely to be successful, although in two instances I have applied leeches to the precordia and found that the pain immediately abated. Nitroglycerin is contraindicated and yet patients sometimes take it because they have been in the habit of using it for attacks of angina pectoris. If the heart should stop suddenly and the doctor is at the bedside, he might resort to an intracardiac injection of 1 cc. of adrenalin chlorid 1 to 1000 solution. Under ordinary circumstances adrenalin and probably ephedrin are contraindicated in patients with angina pectoris and coronary occlusion. The dangers of the use of adrenalin in angina pectoris and coronary sclerosis have been pointed out by Levine, Ernstene and Jacobson,[13] and by Cottrell and Wood.[14]

Another agent of value in my experience is glucose or sugar. The glucose can be given intravenously. I have been in the habit of ordering ginger ale, water-ice, apple sauce, pineapple juice and orange juice for the purpose both of supplying fluid and of supplying sugar.

Levy has recommended oxygen inhalations during the acute attack. I have used them, employing the well-known oxygen tent

for the purpose. The patients were made more comfortable but I have not seen that the procedure had any effect as regards saving life.

A question that nearly always comes up is—Shall digitalis be used? Having in my mind's eye the pathologic condition of the heart in acute coronary occlusion—infarction with softening—I have been afraid of using digitalis in adequate doses and I am glad to see that that is the opinion of most writers. If, however, there is auricular fibrillation or congestive failure as a sequel of the coronary attack then digitalis is indicated as it would be if coronary occlusion had not occurred.

If cardiac stimulation is necessary and very frequently it is demanded, my favorite remedy is caffein sodiobenzoate hypodermically, using an ampule containing 0.5 gm. (7½ grains) of the drug. When conditions are less pressing, the caffein sodiobenzoate may be given by mouth in doses of 0.12 to 0.20 gm. (2 to 3 grains).

If diabetes exists insulin should be withheld as it is dangerous in cases of coronary occlusion. Its use would only be justified in threatening coma.

How long should the patient stay in bed? From 5 to 6 weeks is the minimum in a severe case of coronary occlusion. A cardiac scar is thought to be firm after 8 weeks. It may not be wise to tell the patient at the beginning of his incarceration the length of the sentence. The tactful physician will achieve his end by giving an answer which is true but not necessarily specific. The getting-up process should be gradual and so should be the resumption of the ordinary vocations and avocations of life. The man who has had a coronary occlusion should avoid physical strain and should not indulge in competitive athletics. I am also averse to permitting such patients to drive their own cars, although one may have to make concessions in keeping with the patient's circumstances.

The post-thrombotic or interval treatment has been in the main covered in the foregoing section. A few additional suggestions may now be given. Of greatest importance is encouragement. Psychotherapy, of enormous help in most diseases, is of transcendent value in patients who have had anginal or thrombotic attacks.

The diet should be sensible and restricted in quantity if the patient has been habitually a big eater. A little whisky may be allowed to the man who has been accustomed to drinking alcohol.

Drugs are not of much moment. Whether the euphyllin derivatives are of any value in dilating the coronary vessels, as is believed by many or, more properly speaking, is stoutly maintained by the manufacturers, is still a moot question. Until more exact knowledge is available, I shall, however, continue ordering for short periods at a time one or two tablets of metaphyllin or similar product a day. I also believe that small doses of digitalis, 5 or 10 drops thrice daily, are useful.

The patient who has had a genuine attack of coronary thrombosis must ever after shape his life in accordance with his narrowed limitations. He should not exert himself unduly and should cease playing golf, tennis or similar active sports. Short business hours and a long postprandial siesta are very desirable, and a 5-day week is an excellent thing for the coronary individual. If economic conditions permit the patient should take a winter as well as a summer vacation. Many spend their vacations unwisely. Instead of resting they work just as hard only in a different way.

I believe men who have been heavy smokers should reduce their smoking to a minimum or better give it up entirely.

Re-examination at fairly frequent intervals, including electrocardiographic study, is important in discovering any signs of cardiac weakness.

TABLE 5.—PERSONAL CASES OF CORONARY THROMBOSIS.

Number of cases (men 74, women 14)	88	Tobacco chewers	2
Number of cases living	38	Tobacco habits not recorded	24
Number of cases dead	34	Non-users of tobacco	16
Number of cases unknown	16	Family history of heart disease or hypertension	24
Greatest duration of life after onset of those known to be living	16*	No heart disease known	41
Greatest duration of life after onset of those known to be dead	11*	Definite negative history of heart disease	23
Average age of onset (youngest 32, oldest 81)	57*	Occupations—men:	
Hypertension (5 blood pressures not recorded)	49	Merchants	18
Pericardial friction	7	Manufacturers or executives	18
Typhoid fever	7	Physicians	10
Renal calculi	7	Bankers	4
Rheumatism	7	Salesmen	3
Diabetes	4	Clerks	3
Syphilis	3	Lawyers	3
Polycythemia	2	Brewers	2
Used tobacco (excessively 22)	46	Various (1 each)	13
Cigarette smokers	20	Occupations—women:	
Cigar smokers	16	Housewives	10
		Nurse	1
		No occupation	3

* Years.

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THE LARGE Q WAVE IN LEAD III OF THE ELECTRO-CARDIOGRAM.

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I. Introduction. The following observations are based upon an analysis of 103 electrocardiograms characterized by a normal sinus rhythm with a significant Q wave in Lead III selected from records taken in this cardiac clinic during the past 5 years. In addition, there are presented the pathologic alterations in the heart in those cases that came to autopsy. An attempt is made to correlate these lesions with the changes observed in the electrocardiogram.

Pardee,[9] in 1920, published the first analysis of the R-S-T interval in a clinical case of coronary occlusion and, at the time, noted a conspicuous Q wave in Lead III. This association was again discussed in the first edition of his book[10] and, since then, has been observed by others.[6,12,16] It was not until 1930, however, that Pardee[11] stressed the high incidence of angina pectoris in those patients whose electrocardiograms contained a deep Q_3 and emphasized the rarity of this wave in the records of normal, young adults. Further observations on the subject have since appeared.[3,4,14]

That a conspicuous Q wave in Lead III is frequently associated with coronary sclerosis and myocardial disease may be seen from the analyses published by various authors. Willius[14] found that out of 300 cases showing this wave, 38 per cent gave a history of angina pectoris and that 89 per cent could be grouped as having angina, hypertension or chronic, non-valvular heart disease. Pardee's series[11] of 43 instances with Q waves gave a history of angina pectoris in 63 per cent of the cases, while 77 per cent fell into the group including angina, hypertension and chronic, non-valvular heart disease. Edeiken and Wolferth,[3] in 75 cases, and Ziskin, in 86 cases, found the incidence of angina to be 29 per cent and 14 per cent respectively, while 55 per cent and 65 per cent of the cases fell into the group including angina, hypertension and chronic, non-valvular heart disease.

Although Krumbhaar and Jenks[5] observed a conspicuous Q_3 as a common finding in the electrocardiograms of infants between the ages of 2 and 12 months, the rarity of this wave in the records of normal, young adults is evident. In 277 cases with normal hearts Pardee[11] found a large Q_3 in only 2 instances. Edeiken and Wolferth[3] in the records of 709 apparently normal college students found none which showed a significant Q wave in Lead III. The same authors

examined the electrocardiograms of 117 athletes of the University of Pennsylvania and found a large Q_3 in only 1 case. From the above observations the calculated incidence of a significant Q_3 in the electrocardiograms of normal, young adults is 0.27 per cent.

On the other hand, a conspicuous Q wave in Lead III has been found to occur in the records of patients who show, in the absence of cardiac signs or symptoms, an elevated diaphragm with lateral displacement of the cardiac apex.[3,11,17] In a small percentage of cases this wave is present in the records of women during the 8th month of pregnancy and disappears after delivery. Similarly, changes in the cardiac axis during respiration occasionally cause, in Lead III, the appearance of a Q wave which varies in size with the different phases of the respiratory cycle and is frequently associated with flattening or inversion of the P and T waves. Ascites, obesity and a wide costal angle all predispose toward a high diaphragm and a transverse cardiac axis. In the average series, the occurrence of this complication appears, at first glance, to be relatively infrequent. However, coronary sclerosis, hypertension and myocardial disease occur commonly in elderly, obese, thick-set individuals. In such cases the influence of lateral displacement of the cardiac apex upon the initial deflection of the Q-R-S complex in Lead III must be considered.

In summary, then, the accumulated evidence indicates that the deep Q wave in Lead III is significant as an electrocardiographic abnormality because of its rarity in the records of normal, young adults and the frequency with which it is found in association with heart disease. As a complicating factor, the part played by lateral displacement of the cardiac apex, although usually uncertain in the individual case, would seem to be important.

II. Analysis of Electrocardiograms. Out of 3600 patients included in the electrocardiographic examinations for the past 5 years, there were 103 who were over the age of 12, who had complete histories available and whose records were characterized by a normal sinus rhythm with a significant Q wave in Lead III.

In the selection of significant Q waves the following standards were used: (1) an initial, downward deflection of the Q-R-S complex in Lead III; (2) this deflection to be not less than 25 per cent of the greatest excusion of the Q-R-S in any lead; (3) the downward deflection (Q) to be followed by a definite upward deflection (R), without a subsequent S wave; (4) the absence of right axis deviation. These, essentially, are the criteria set down by Pardee in his original article.[11]

The histories of the 103 cases were then studied and note made as to the presence or absence of angina pectoris, hypertension and myocardial insufficiency. In addition, any mention of a syphilitic infection or a previous history of rheumatic fever was recorded. Substernal pain or oppression, brought on by exertion and relieved

by rest or nitrites, was taken as the criterion of angina pectoris. The substernal pain occurring in cases of hypertension or coronary occlusion was included as part of the anginal syndrome. A diastolic pressure of over 100 mm. of Hg in the presence of a systolic pressure above 150 mm. of Hg was taken as evidence of hypertension. Myocardial insufficiency was considered present when, in the absence of other contributing causes, there was moisture at the bases of the lungs posteriorly, edema of the lower extremities, or dyspnea and palpitation with slight exertion.

TABLE 1.—ANALYSIS OF CARDIAC SIGNS AND SYMPTOMS IN 103 CASES SHOWING A LARGE *Q* WAVE IN LEAD III.

Clinical diagnosis.	Cases.
Anginal syndrome	46 (45%)
Hypertension without anginal syndrome	19 (18%)
Chronic, non-valvular heart disease without hypertension or anginal syndrome	16 (16%)
Absence of cardiac signs or symptoms	9 (9%)
Postoperative dyspnea and tachycardia	3
Hyperthyroidism	2
Neurocirculatory asthenia	2
Subacute bacterial endocarditis	1
Pneumonia	1
Acute rheumatic fever	1
Chronic bronchitis	1
Syphilitic aortitis with aortic aneurysm	1
Syphilitic aortitis with aortic insufficiency	1
	103

NOTE.—Of the 103 cases in the present series, 27 were private patients and 76 were seen on the wards or in the clinic. The incidence of angina pectoris in the group of private patients was 59 per cent, while the same symptom occurred in 39 per cent of the ward and clinic patients. The incidence of a positive Wassermann reaction was 12 per cent for the total series and 4 per cent of all the cases gave a history of rheumatic fever.

The comparison of these figures with those obtained by other investigators is seen from the following:

TABLE 2.—ANALYSIS OF CASES WITH LARGE *Q* WAVES AS FOUND IN THE LITERATURE.

	No. of cases.	Angina pectoris, per cent.	Angina, hypertension, or chronic, non-valvular heart disease, per cent.	Absence of cardiac signs or symptoms, per cent.
Pardee	43	63	77	0
Willius	300	38	89	1
Edeiken and Wolferth	75	29	55	9
Ziskin	86	14	65	23
Present series	103	45	79	9

III. Associated Changes in the Electrocardiogram. The next attempt, in the present study, was to determine whether or not certain electrocardiographic changes indicative of myocardial damage bore any relation to the incidence of coronary and myocar-

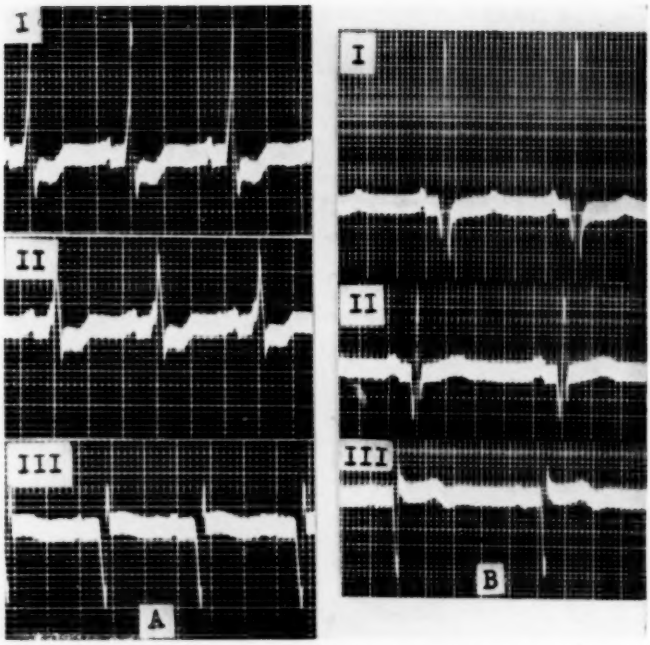

FIG. 1.—Records with large Q waves in Lead III. *A*, syphilitic aortitis with aortic insufficiency and occlusion of the right coronary orifice. Digitalis. Autopsy No. 13000. *B*, a case of angina pectoris with blood pressure at the upper limit of normal. No digitalis.

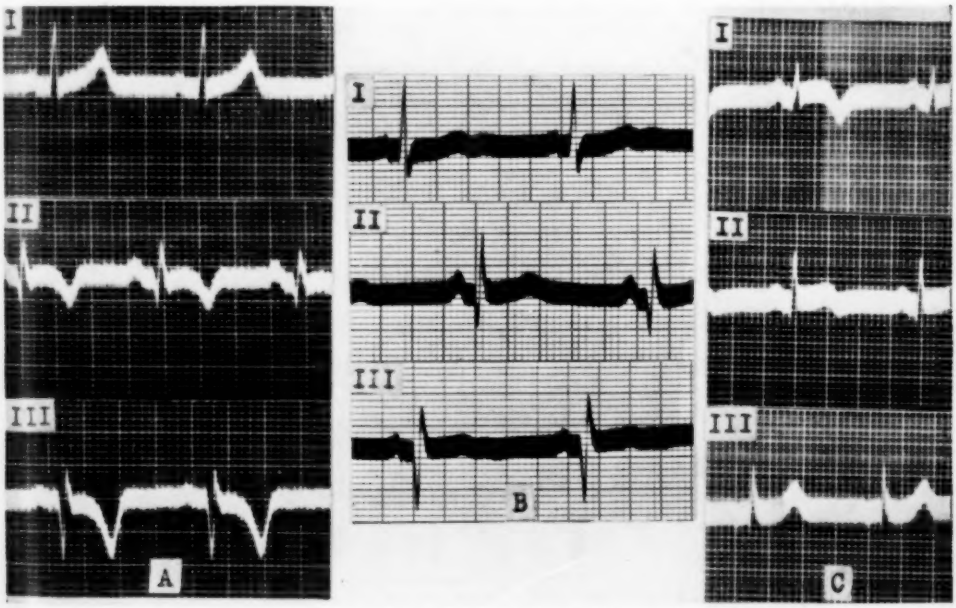

FIG. 2.—Records typical of the three groups of undigitalized patients classified in Table 3. *A*, deep Q_3 with sharply inverted T waves in Leads II and III. *Group I*. *B*, a large Q_3 in an otherwise normal electrocardiogram. *Group II*. *C*, no Q wave in Lead III. Sharply inverted T wave in Lead I and biphasic T wave in Lead II. *Control group*.

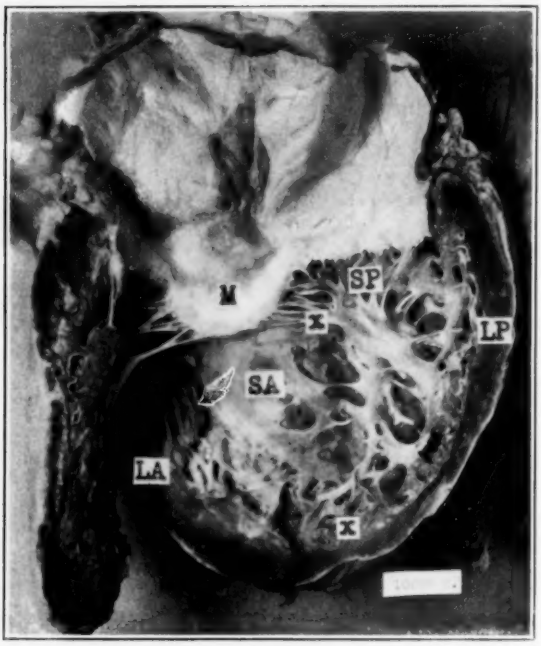

FIG. 3.—Autopsy No. 10888. Heart showing infarction of posterior portion of left ventricle and interventricular septum as the result of right coronary artery occlusion. *LA*, anterior wall of left ventricle; *LP*, posterior wall of left ventricle; *SA*, anterior half of interventricular septum; *SP*, posterior half of interventricular septum; *X–X*, margin of infarct in interventricular septum; *M*, mitral valve.

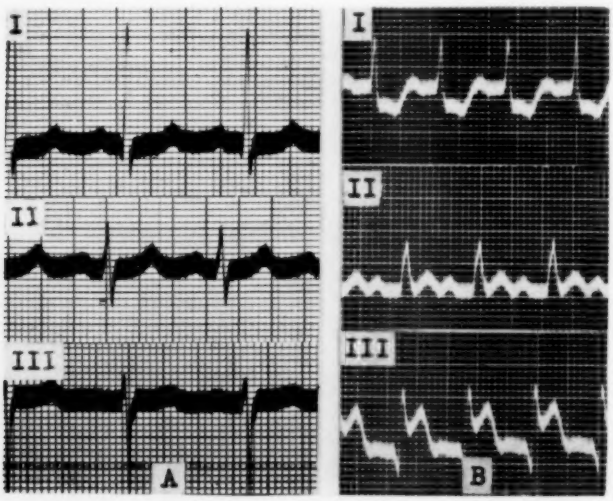

FIG. 4.—Autopsy No. 12271. *A*, record taken April 9, 1930. Left axis deviation with prominent *S* wave in Lead III. *B*, record taken November 10, 1931, several hours after the onset of an attack of coronary occlusion. *Q* wave and high take-off of *R-T* interval in Lead III. Autopsy, 12 hours later, showed fresh thrombus in right coronary artery.

dial disease in cases showing a conspicuous Q wave in Lead III. That such a relation might exist is suggested by the findings of Pardee[11] in his series of 43 cases. Here there were 16 who did not have the anginal syndrome and of these there was only 1 whose record contained an abnormal T wave.

Of the 103 patients in the present series, 39 were excluded because of digitalis medication. The remaining 64 were divided into two groups. In the first group were placed the 32 undigitalized patients whose records showed, in addition to a large Q_3, one or more of the following changes: (1) inversion of (*a*) T_1 or (*b*) T_2 and T_3; (2) high or low take-off of the R-S-T interval in Leads I or III; (3) slurring at the apex of R_1 or S_1. The second group consisted of the remaining 32 undigitalized cases with records showing a deep Q_3 but an otherwise normal Q-R-S-T complex. As a control series, there were selected 32 undigitalized patients whose records, in the absence of a Q wave in Lead III, showed the above mentioned changes indicative of myocardial disease.

TABLE 3.—THE RELATIVE INCIDENCE OF CERTAIN CARDIAC SIGNS AND SYMPTOMS IN AN UNDIGITALIZED GROUP OF CASES SHOWING A LARGE Q WAVE IN LEAD III.

	Group I. Q_3 + other ekg. changes.	Group II. Q_3 alone.	Control group. No Q_3 other ekg. changes as in Group I.
Number of cases	32	32	32
Angina pectoris	23 (72%)	3 (9%)	12 (38%)
Signs and symptoms of acute coronary occlusion	6 (19%)	0	2 (6%)
Hypertension	9 (28%)	6 (19%)	16 (50%)
Absence of cardiac signs or symptoms	0	8 (25%)	2 (?)

NOTE.—Of the 2 cases in the control group listed as being without cardiac signs or symptoms, 1 had syphilis and a possible syphilitic aortitis, while the other was a neurotic woman who showed no cardiovascular abnormalities on physical examination but who gave a history of dyspnea, edema of the ankles and attacks of precordial pain.

The statistics presented in Table 3 suggest that in a group of undigitalized patients, whose records are characterized by a conspicuous Q wave in Lead III, those cases in which additional evidence of myocardial damage appears in the electrocardiogram may be expected to show a high incidence of angina pectoris. On the other hand, in those instances in which the large Q_3 is the only electrocardiographic abnormality, angina pectoris will be much less frequently encountered and a certain proportion of the cases will be without demonstrable cardiac disease.

IV. Postmortem Findings. Of the 103 patients in the present series, 12 came to autopsy (Table 4). On the basis of changes found in the coronary arteries and in the myocardium, the cases were divided into three groups: (1) those showing no significant narrowing of the coronary arteries; (2) those showing narrowing or

occlusion of one or more coronary arteries but no gross infarction of the myocardium; and (3) those showing, in addition to coronary occlusion, a circumscribed area of infarction characterized by gross scarring and thinning of the myocardial wall. In the 4 cases without visible scars, blocks for microscopic study were cut from the anterior apex and the posterior base of the left ventricle. Sections were stained with hematoxylin and eosin and note made as to the presence or absence of perivascular and myocardial scarring.

Three of the 12 cases fell into the first group (Nos. 11853, 12972, 13100). Two of these had a history of hypertension and renal insufficiency. The third was a case of hypertension and polycythemia vera with a terminal miliary tuberculosis. In none was there definite evidence of impairment of the coronary circulation.

In the second group there were 4 cases (Nos. 12024, 12271, 12825, 13056). Three showed marked narrowing of the right coronary artery at some point along its course. The fourth was a case of subacute bacterial endocarditis with a mass of vegetations obstructing the orifice of the left coronary artery. In addition, 2 of the 4 showed marked sclerosis and narrowing of the anterior descending branch of the left coronary artery. There was, however, no evidence of gross myocardial infarction in any of the cases in this group, although in one instance there were many small, linear scars scattered through the myocardium of the interventricular septum.

The third group consisted of 5 cases (Nos. 10745, 10888, 10942, 12802, 13000). In each there was thrombosis of the right coronary artery with infarction of the posterior base of the left ventricle and adjacent portion of the interventricular septum. In two instances the infarct extended to the apex. With the exception of one case, in which a fresh thrombus was considered to be a terminal event, there was no evidence of thrombosis of the anterior descending branch of the left coronary artery or infarction of the area supplied by this vessel.

V. Mechanism. Lewis[7] considered that the initial deflection of the *Q-R-S* complex was the result of activation of the interventricular septum and it is on the basis of changes in this region of the heart that most of the theories concerning the origin of the *Q* wave in Lead III arise.

That a significant Q_3 may occur in the records of patients without demonstrable coronary disease is evident. The results of the present study do not throw any light upon the origin of this wave in such cases. However, the instability of Lead III has been emphasized.[2] Reference is also made to articles by Ziskin,[17] Edeiken and Wolferth,[3] Meek and Wilson,[8] Pardee[11] and Proger[13] for a discussion of the part played by lateral displacement of the cardiac apex and rotation of the heart around its longitudinal axis in shaping the initial deflection of the *Q-R-S* complex in Lead III.

In contradistinction to the cases without demonstrable coronary

TABLE 4.—POSTMORTEM FINDINGS.

Autopsy No.	Age, yrs.	Sex.	Race.	Angina pectoris.	Hypertension	Interval between ekg. and autopsy.	Heart weight, gm.	Condition of coronary arteries.	Condition of myocardium.
11853	29	F	C	0	+	9 dys.	680	No appreciable sclerosis	Great hypert. of left vent.; no gross visible scarring; micro., a few small perivascular scars.
12972	62	M	W	+	+	2 dys.	610	Moderate sclerosis; no definite narrowing of lumina	Hypert., particularly of left vent.; no scars visible in gross; micro., an occasional perivascular scar in ant. wall of left vent.; focal myocardial scars in mod. number in post. wall of left vent.
13100	65	F	W	0	+	2 yrs., 3 mos., 13 dys.	460	Orifices patent, lumina sclerotic but not greatly narrowed	Marked hypert. of left vent.; rather numerous minute scars scattered throughout myocardium of left vent.
12024	22	F	W	0	0	2 mos., 12 dys.	500	Subac. bacterial endocarditis with aortic insuff. and vegetations on aortic valve; orifice of left artery partially occluded by a mass of vegetations; no coronary sclerosis; in gross, no thrombi seen in any coronary arteries	Mod. card. hypert.; small, grayish scars in myocardium; no gross area of infarc. or thinning of myocardium; micro., many small infected infarcts as result of bits of vegetation plugging some arterioles.
12271	53	M	W	+	+	9 hrs.	400	One branch of ant. descending portion reduced to fibrous cord without a patent lumen; only slight sclerosis of remainder of left coronary; marked sclerosis of right coronary with a fresh thrombus just proximal to post. margin of intervent. septum	Slight hypert. of left vent. with many small scars throughout the myocardium, esp. in region of apex; no visible infarc. of left vent. or intervent. septum.
12825	68	F	C	+	0	21 dys.	280	Almost complete occlusion, by an atheromatous plaque, of right coronary just at post. margin of intervent. septum; only slight sclerosis of left and remainder of right	A small heart; no areas of infarc.; no scarring of myocardium visible in gross; a roughened patch on endocardial surface of left auricle; micro., a few small and medium-sized fibrous scars in myocardium of left vent.
13056	62	F	W	+	0	11 mos., 20 dys.	380	Distinct narrowing of right orifice by atherosclerosis; patent left orifice but almost complete occlusion of mouth of anterior descending branch by a calcified plaque	Thickened, fibrous epicardium; no visible areas of infarc.; no myocardial scars visible in gross; micro., many small linear scars in wall of left vent. near endocardial surface.
10745	41	M	W	+	0	20 dys.	480	Slight sclerosis of left, extreme of right, with occlusion by a thrombus just proximal to post. margin of septum	Area of infarc., with thinning and scarring of myocardium, at the post. base of left vent. and intervent. septum.
10888	61	M	W	0	+	3 mos., 27 dys.	600	Sclerosis and calcification of both arteries; no great narrowing of lumina except in case of right; thrombosis of right coronary at one point	Hypert. and dil. of both vent.; slight myocardial scarring in ant. wall of left vent.; area of infarc., with gross scarring and thinning of myocardium in post. wall of left vent. and adjacent portion of intervent. septum (Fig. 3).
10942	20	M	W	+	0	1 mo., 8 dys.	720	Aortic insuff. with large, friable vegetations on aortic valve; left coronary orifice patent; no sclerosis or occlusion of left coronary; thrombosis of right artery (embolus?) several cm. proximal to post. margin of septum	Extreme hypert. and dil. of left vent.; large area of infarc. hollowing out muscle in post. wall of left vent. and adjacent portion of intervent. septum; no other visible scars in myocardium.
12802	63	M	W	+	0	5 dys.	400	Sclerosis of both arteries with narrowing of lumina; old, partially canalized thrombus obstructing lumen of right artery just proximal to post. margin of septum; a fresh thrombus present in the already narrowed lumen of ant. descending branch	Many small scars throughout myocardium of left vent.; area of infarc. at post. base of left vent. and intervent. septum.
13000	45	F	C	0	0	16 dys.	520	Syph. aortitis and aortic insuff.; patent left coronary orifice; slight sclerosis of left artery; complete occlusion of right orifice by syph. aortitis and superimposed thrombus; remainder normal.	Infarc. of myocardium at post. base of left vent. and intervent. septum; restriction of affected area to endocardial half of muscle wall.

disease are those with clinical evidence of coronary thrombosis and records which show a deep Q_3 in addition to the changes characteristic of myocardial infarction. In the present series there were 10 such cases. In each instance the large Q wave was associated with an elevation of the R-T interval in Lead III or with inverted, "coronary" T waves in Leads II and III. Six of the 10 patients came to autopsy and, in all but 1, thrombosis of the right coronary artery was found. The exception (No. 13056) showed partial occlusion of both the right and the anterior descending branch of the left coronary arteries but there were no scars visible in the gross. Four of the 6 cases had, in addition, infarction of the posterior base of the left ventricle and adjacent portion of the interventricular septum. In a fifth instance death occurred 6 hours after the clinical onset of the attack. Autopsy (No. 12271) revealed a fresh thrombus in the right coronary artery but no gross evidence of myocardial infarction.

The finding, in cases of coronary thrombosis, of a large Q_3 in association with an elevation of the R-T interval in Lead III or with inverted, "coronary" T wave in Leads II and III is in accord with the observations of Parkinson and Bedford.[12] The fact that such curves are characteristic of right coronary artery occlusion was first stated by Barnes and Whitten[1] in 1929. Wilson, Barker, Macleod and Klostermeyer[15] have recently reported similar findings. In addition, Fenichel and Kugell,[4] studying the relation of the large Q wave in Lead III to myocardial disease, observed infarction or diffuse scarring of the posterior portion of the interventricular septum in a series of 12 cases whose records showed left axis deviation and a conspicuous Q_3.

It would seem, therefore, that occlusion of the right coronary artery with infarction of the posterior base of the interventricular septum would, in certain cases, constitute an important factor in the production of a large Q wave in Lead III. Whether or not partial occlusion of the same artery is capable of producing a similar electrocardiographic change seems, at present, uncertain and may depend upon the extent of the collateral circulation. Finally, it is important to consider that in association with coronary disease, the factors which produce a deep Q_3 in cases with normal hearts may be present and complicate the interpretation of the record.

VI. Summary. An analysis is made of 103 electrocardiograms characterized by a normal sinus rhythm with a significant Q wave in Lead III.

A study of the histories of the above cases with reference to the electrocardiographic findings is presented.

The pathologic alterations in the hearts of 12 of the cases are given.

The relation of the Q wave mechanism to occlusion of the right coronary artery and infarction of the posterior basal portion of the interventricular septum is discussed.

The results of the present study are in accord with the observations of others[3, 4, 11, 14, 17] to the effect that the large Q wave in Lead III, while sometimes present in the absence of heart disease, is frequently associated with serious myocardial damage. Furthermore, it is indicated that when this wave and additional evidence of myocardial disease exist in the record, angina pectoris is often present. Postmortem findings support the view that the deep Q_3 is commonly seen as part of the evidence of the electrocardiographic change occurring after thrombosis of the right coronary artery with subsequent infarction of the posterior base of the left ventricle and adjacent portion of the interventricular septum.

NOTE.—I am deeply indebted to Drs. E. P. Carter and A. R. Rich for their helpful advice and criticism. I also wish to thank Miss J. A. Vickers for her assistance in preparing the photographs of the electrocardiograms. The photograph of the pathologic material was taken by Mr. M. Kougl.

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THE EFFECT UPON THE ELECTROCARDIOGRAMS OF PATIENTS WITH REGULAR SINUS MECHANISM OF QUINIDIN SULPHATE.

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IN the routine clinical interpretation of electrocardiograms it is obviously essential to know the effect of various modifying factors, particularly drugs, which change the character of the curves. In

a case of suspected coronary thrombosis, complicated by a paroxysm of tachycardia, the question recently arose as to whether the *T* wave changes were a result of the suspected occlusion or a result of the administration of quinidin sulphate. To clarify this issue, a survey was made of the literature regarding the effect of this drug, and a series of studies were made to substantiate the reported data.

A review of the literature revealed no specific studies of the effects of quinidin sulphate on the electrocardiograms of the patients with normal sinus mechanisms. There was little information regarding the effect of the drug upon any specific mechanisms, other than the studies of Lewis of its action upon the fibrillating auricles. Pardee states in his text that quinidin tends to change the form of the *P* wave, probably by displacing the site of impulse from its normal place in the sinus node. Furthermore, it causes a prolongation of the *Q–R–S* group and a greater prolongation of the *T* wave —evidences of the powerful effect of this drug in delaying the spread of the contraction and the process of the contraction itself. He states also that it produces an abnormal inversion of the *T* wave. According to Pardee, the drug has not received such careful study as digitalis. Lewis makes the general statement that the alkaloid quinidin depresses conduction in all the muscular tissues of the heart, as evidenced by increased *A–V* conduction and widening of the *Q–R–S*. Many authors, such as Jenny, Singer, Frey, Martin, Cheiniesse, Fahrenkamp, and Schott, casually mention the flattening and inversion effect on the *T* wave, widening of the *Q–R–S* and prolongation of the *A–V* conduction.

Summary of the published work would imply that quinidin changes the *T* wave and prolongs *A–V* and intraventricular conduction, with no specific data with reference to dosage or time effects.

The studies made in this report were carried on in a general medical ward of the Cook County Hospital, Chicago. In the first group of cases 10 patients were selected and quinidin sulphate was administered orally in 10-grain doses, 3 times in 24 hours; at 8 A.M., 4 P.M. and 12 midnight. Daily electrocardiograms were taken between 7 and 8 P.M., with 1 or more control electrocardiograms before any drug was given. All other forms of medication were eliminated. Three other cases were selected for study and quinidin sulphate was administered during 2 minutes intravenously in doses of 3 grains dissolved in 20 cc. of distilled water; electrocardiographic tracings were taken from a lead from the chest wall from the 2d and 5th interspaces. Another 3 patients were treated in the same way, except that the regular 3 leads were taken. Another group of 3 patients was given quinidin sulphate, 15 grains, q.i.d., or a total of 60 grains per 24 hours. The data collected from these studies are shown in Charts I, II, III and IV.

Discussion. In determining the changes produced in electrocardiograms from any given factor, it is necessary to consider the variations that occur without evident cause. In our experience routine daily curves frequently show minor variations, particularly in the contour of the *P* waves, such as notching and rounding and slight change in heights. The *Q–R–S* may vary slightly in contour, as well as the *R–T* or the *S–T* segment. In diphasic *T* waves it is not uncommon to note mild changes in the character of these waves; therefore, no changes were accepted as evidence of the effect of the drug unless they were consistently present and unless they disappeared on elimination of the drug.

With the dose of 30 to 60 grains per day, which was used as an average amount used therapeutically, no consistent changes were observed in the character of the *P* waves in any lead (Chart I). The *Q–R–S* complexes furthermore showed no appreciable change in time, duration, character or height. The *P–R* intervals remained the same. The only consistent definite deviation was in the effect upon the *T* waves. In 1 case (7.5 per cent) there was a marked flattening; in 2 cases (15 per cent) no appreciable change and in 10 cases (85 per cent) a mild to moderate flattening. The *R–T* or *S–T* segments apparently did not participate in this change as they do in digitalis. It is interesting to note that the greatest change in the character of the *T* waves was in those which were originally high and pointed.

The cases in which no appreciable or minor effects were noted were those in which the *T* wave was either diphasic or low. This evidence of organic change is substantiated by the clinical diagnosis of tabes, terminal endocarditis, malignancy and prolonged *A–V* conduction time. One case had previously received digitalis for several weeks.

The effect of the drug was noted in from 12 to 72 hours, with an average time of 48 hours. The disappearance of the *T* wave deformity was usually in a few days; we were unable to secure information on this point in all the 13 cases. After the *T* wave effect was noted, continued administration of the same dose did not seem to produce any greater effect. The maximal period of observation was 19 days, and in this case the *T* wave became isoelectric in 48 hours and remained so. The characteristic change is shown in Fig. 1.

Chart II shows the data collected when the quinidin sulphate was administered intravenously, and a lead taken directly from the chest wall at the 2d and 5th interspace to the right of the sternum. There were no demonstrable changes in the *P* waves, *P–R* intervals or *Q–R–S* complexes. As a matter of fact, the complexes before and after taking may be superimposed one upon another accurately, so that measurements were not required. The *T* waves only were affected and a small portion of the *R–T* or *S–T* segment.

CHART I.—EFFECT OF QUINIDIN GIVEN ORALLY (30 GRAINS DAILY).

Case No. and initials.	Diagnosis.	Days of dosage.	Control of EKG. findings.	Changes in EKG. after quinidin.	Time of appearance, hrs.	Time of disappearance.	Remarks.
1. T. Mc.	Arteriosclerosis; hypertension; chronic arthritis	5	*P–R* int. 0.2 sec.; left axis deviation; *Q–R–S* slurred in all leads; extrasystoles of auricular origin; *T* waves upright in I and II and inverted in III	Moderate flattening of *T* waves in I and II; isoelec. in III	36	6 days	Extrasystole disappeared.
2. J. H.	Duodenal ulcer	8	*P–R* int. of 0.26 sec.; left axis deviation; diphasic *P* in III; *T* waves upright in all leads	Mild flattening of *T* waves; most marked in II and III	12	Left hospital	None.
3. T. G.	Carcinoma of esophagus	19	*P–R* int. of 0.18 sec.; *Q–R–S* upright in all leads, but low in I; slurred *R* near base line in II and III; *T* waves all upright	Isoelectric *T* waves in all leads	48	4 days	None.
4. H. J.	Tabes dorsalis	8	*P–R* int. of 0.2 sec.; *Q-R-S* notched in III; diphasic *T* waves in all leads; notched *P* in III	No appreciable change	...	...	None.
5. N. R.	Teratoma of testis with metastases	8	*P–R* int. of 0.16 sec.; *Q–R–S* diphasic in I and upright in II and III; *T* wave upright in I, low in II and isoelectric in III	Very mild rounding of peaks of *T* waves	72	Impossible to determine	None.
6. J. J.	Duodenal ulcer	9	*P–R* int. of 0.18 sec.; *Q–R–S* upright in all leads; *Q–R–S* notched in III; *T* waves upright in I and II and diphasic in III	Moderate flattening of *T* waves in I and II	36	4 days	None.
7. G. G.	Arteriosclerosis	9	*P–R* int. of 0.16 sec.; *Q–R–S* mildly slurred, upright in I, diphasic in I and III; *T* waves upright and broad in I and II and low in III	Moderate flattening in all 3 leads	48	4 days	None.
8. J. L.	Ulcerative colitis	8	*P–R* int. of 0.16 sec.; *Q–R–S* upright in all leads; high pointed *T* waves in I and II and low in III; absent *R–T* segments	Moderate flattening in all 3 leads	48	3 days	None.
9. H. A.	Duodenal ulcer	8	*P–R* int. of 0.18 sec.; *Q–R–S* upright in all leads; sinus bradycardia (50); notched *R* in III; *T* waves high and pointed in I and II and low in III	Moderate flattening in all 3 leads	48	Left hospital	None.
10. A. P.	Carcinoma of bowel	6	*P–R* int. of 0.16 sec.; left axis deviation; *Q–R–S* notched in III; *T* waves upright in all leads	Moderate flattening of *T* waves in all	48	4 days	None.

CHART II.—EFFECT OF QUINIDIN GIVEN INTRAVENOUSLY (3 GRAINS).

Case No. and initials.	Diagnosis.	Control EKG. findings.	Changes in EKG. after quinidin.	Time of appearance.	Time of disappearance.	Remarks.
11. F. H.	Convalescent pneumonia	*P–R* int. of 0.16 sec.; *Q–R–S* downward, mildly slurred; *T* wave broad but pointed	*T* wave became isoelectric	2 min. from beg. of injection	*T* wave still flattened after 1 hr. 35 min.	No change in bloodpressure.
12. W. K.	Tuberculosis of cecum	*P–R* int. of 0.16 sec.; *Q–R–S* diphasic, mildly slurred; *T* wave sharply upright	*T* wave became sharply inverted	*T* wave isoelectric in 1 min. 30 sec.; inverted in 2 min.	*T* wave still flattened in 2 hrs. and 8 min.	No change in bloodpressure.
13. C. F.	Arteriosclerosis	*P–R* int. of 0.18 sec.; *Q–R–S* diphasic, mildly slurred; *T* waves sharply upright	*T* wave became almost isoelectric	Unknown	Peak of *T* wave still flattened in 2 hrs. 13 min.	Bloodpressure dropped from 150/60 to 140/60 then 124/60 and back to 144/68.

CHART III.—EFFECT OF QUINIDIN GIVEN INTRAVENOUSLY (3 GRAINS).

Case No. and initials	Diagnosis.	Control EKG. findings.	Changes in EKG. after quinidin.	Time of appearance.	Time of disappearance, hrs.	Remarks.
14. H. L.	Gastric ulcer	*P–R* int. of 0.16 sec.; *Q–R–S* upright in all leads; *T* waves sharp and upright in I and II and flattened in III	*T* wave markedly flattened in I and II and isoelectric in III	Less than 7 min.	3	Bloodpressure dropped from 155/90 to 135/90.
15. C. C.	Moderate hypertension; arteriosclerosis	*P–R* int. of 0.18 sec.; *Q–R–S* upright in I, diphasic in II and III and slightly slurred; *T* wave pointed and upright in all leads	*T* waves mildly flattened in all leads	Less than 5 min.	2	Bloodpressure dropped from 140/70 to 128/64.
16. D. J.	Arteriosclerosis; hypertension; cardiac hypertrophy	*P–R* int. of 0.26 sec.; marked left axis deviation; mild slurring of *Q–R–S*; *T* waves upright and broad in I, isoelectric in II and sharply down in III; vent. premature contr.	*T* wave in I isoelectric; no change in II; in III *T* wave became isoelectric	Less than 5 min.	3	Bloodpressure dropped from 152/68 to 130/78; ventricular extrasystoles disappeared

CHART IV.—EFFECT OF LARGER DOSES OF QUINIDIN GIVEN ORALLY (60 GRAINS DAILY).

Case No. and initials.	Diagnosis.	Days of dosage.	Control EKG. findings.	Changes in EKG. after quinidin.	Time of appearance, hours.	Time of disappearance.
17. F. E.	Chronic colitis	6	*P–R* int. of 0.14 sec.; mildly slurred *Q–R–S*: sinus mech.; *T* wave up in all leads	Moderate flattening of *T* waves in all leads	24	Unknown.
18. A. R.	Bronchial asthma	13	Sinus mech.; right axis deviation; iso-elect. *T* wave in all leads; concave *R–T* segment	No change in 13 days; *T* wave and *R–T* segment deformed by digitalis	....	Digitalis taken preceding quinidin régime.
19. H. G.	Perigastric adhesions and gastric ulcer	7	Sinus mech.; *P–R* int. of 0.18 sec.; *T* wave upright in all leads	Moderate flattening of *T* wave in all leads	48	Unknown.

1/10th Second
1/5th and 1/25th Second
Millimeters
Lead No. 1—Between Right and Left Arms
Lead No. 2—Between Right Arm and Left Leg
Lead No. 3—Between Left Arm and Left Leg

FIG. 1.—Case 3. Normal control electrocardiogram to the left and curve taken after 5 days of oral dosage of 30 grains daily to the right.

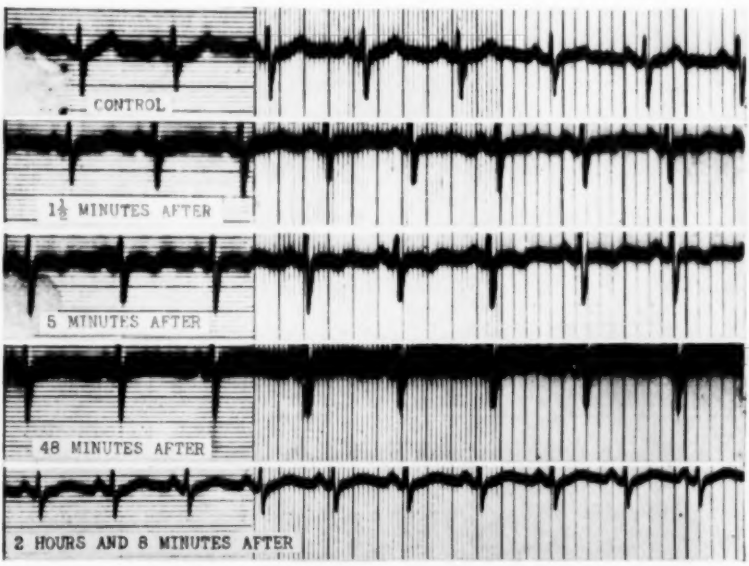

FIG. 2. Case 12. Single chest leads taken after intravenous administration of 3 grains showing gradual change in the contour of the *T* waves.

This experiment only served to corroborate the findings of the oral administration, namely, that the *T* wave is the primary change. The effect appears in 1 to 2 minutes and wears away in a few hours. No general reactions were noted. The characteristic inversion is shown in Fig. 2.

Chart III shows the effects of the drug in the 3 cases on intravenous administration with the regular 3 leads. Two of these cases, C. C. (15) and O. J. (16), were cardiacs, with organic change. The same phenomenon was noted here: that the change was less than those where the electrocardiograms showed no evidence of defective conduction. The effect disappeared within 3 hours.

In Chart IV the results of the oral administration of 60 grains of quinidin sulphate are shown. The electrocardiographic changes were practically the same as in those who received 30 grains per day. With the higher doses, however, complaints of tinnitus and head noises were noted after the second day. One patient (A. R.) had received digitalis for 3 weeks previous to the administration of the quinidin which produced a deformity of the *R–T* segment and *T* wave in the electrocardiogram. The administration of quinidin caused no change in the contour of this curve.

On the basis of our studies with doses of 30 to 60 grains, administered orally over a period of 5 to 19 days, or intravenous injections of 3 to 5 grains, it would not appear that the findings as reported in the literature of changes in the *P* wave, *P–R* interval, or *Q–R–S* complex were verified. The conclusions of *T* wave changes were amply sustained. In discussion of these discrepancies it is our opinion that changes in the contour of the *P* waves may normally occur in any series of electrocardiograms taken over a period of time. In another series of experiments, yet unpublished, of the effects of quinidin sulphate upon the fibrillating auricle, we have found that when intoxication of the cardiac muscle appears with heavy doses such as intravenous injections of 5 grains every 4 hours for 4 doses, or 10 to 12 grains in 1 injection, in some cases there was a lengthening of the *Q–R–S* complex as well as marked notching and slurring, and the appearance of frequent extrasystoles as well as ventricular tachycardia.

It is our belief that changes of the *Q–R–S* are effects of intoxication by the drug rather than effects that one may expect in therapeutic doses.

Summary and Conclusions. 1. Quinidin sulphate was administered to 19 patients, 10 receiving 30 grains orally per day, 3 receiving 60 grains orally per day, and 6, intravenous injections of 3 to 5 grains, with no general toxic effects.

2. The electrocardiograms in the majority of these patients showed changes only in regard to the *T* waves, within 24 to 72 hours if orally administered and immediately if given intravenously.

3. These changes varied from mild flattening to sharp inversion of the T waves.

4. The duration of the effect varied from 3 to 6 days on oral administration and 3 hours on intravenous administration.

5. Changes in the Q–R–S and P–R intervals are presumably effects produced by intoxicating doses.

THE CLINICAL SIGNIFICANCE OF B. COLI HEMOLYTICUS.

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It has been recognized for some time that certain strains of B. coli have hemolytic properties, but there is a difference of opinion as to whether they have any definite clinical significance. Their occurrence in humans is chiefly in the gastro-intestinal and urinary tracts.

Schmidt[1] in 1909 described three different types, viz., those producing a clear broad zone of hemolysis on blood (goat) agar plates, those producing a narrower and not entirely clear zone, and a third type in which there was evidence of hemolysis only beneath the colony. Very recently Paulson and Brown[2] have reported that the colony appearance produced by members of the B. coli group in blood (rabbit) agar are fundamentally the same as those described by Brown for streptococci ranging from the gamma and viridans non-hemolytic types through the alpha prime and beta hemolytic types.

As regards the frequency of their occurrence in stool specimens, Schmidt[1] concluded that there was no difference between the sick and the well. On the other hand Dudgeon, Wordley and Bawtree[3] found hemolytic B. coli in 35 per cent of 21 colitis cases in adults and in 36 per cent of 11 cases of infantile diarrhea, whereas in the stool specimens of 39 normal adults they were recovered in 13 per cent. Todd, quoted by these authors, also found the hemolytic type in 13 instances in stools of 100 infants under 1 year and not suffering from diarrhea. In a later paper Dudgeon,[4] reported that in 200 pathologic cases, typhoid, postdysentery colitis, septic infections of the respiratory tract, hemolytic B. coli were present in the feces in 6 per cent and when present at all they completely or almost completely supplanted the non-hemolytic type. Davidson[5] during

a careful bacteriologic examination of stool specimens from 26 normal adults did not find any B. coli strains which he considered definitely hemolytic. Meyer and Löwenberg[6] agreed with the finding of Dudgeon, *et al.*, that hemolytic B. coli are more frequently present in stool specimens from cases with gastro-intestinal disturbances, as they encountered them in 58 per cent of such cases as contrasted with 25 per cent of normals.

There are few references in the literature to the distribution of hemolytic B. coli in the human intestine. Klingenstein[7] made cultures from 42 early postmortems where the intestines were not obviously diseased and in 55 per cent hemolytic B. coli were found. Of these cases 9 yielded positive cultures from the jejunum, 14 from the ileum and 19 from the colon. As is well known, the colon group tends to grow at unusually high intestinal levels where there is gastric anacidity, and Adler, Sinek and Reimann[8] have reported that in pernicious anemia cases there may occur large numbers of hemolytic B. coli in the stomach and duodenum.

Dudgeon, Wordley and Bawtree[3] in connection with a comprehensive study of urinary infections by the colon group reported that in a series of 91 cases, 76 per cent of the strains isolated from males were hemolytic, whereas in females only 33.7 per cent were of that type. This finding was confirmed by Löwenberg[10] who reported that in a total of 61 cases of pyelitis there occurred 64 per cent infection with hemolytic B. coli among the males and 34.6 per cent among the females. Herrold[11] examined 8 selected cases of pyelonephritis with the object of correlating urinary B. coli strains with fecal strains. In 5 yielding hemolytic B. coli, strains similar by agglutination test with the urine strains were found in the feces or the cervix uteri. He concluded that hemolytic strains have a greater advantage because of virulence than the non-hemolytic but that the latter tend to persist longer. This last suggestion found corroboration in the study of Bitter and Grundel[12] who concluded that hemolytic B. coli strains led to a sudden, severe, but short infection of the urinary tract; whereas with the non-hemolytic strains the onset is gradual and the disease tends to become chronic. Of their 92 cases, 32 (34.8 per cent) yielded hemolytic B. coli. In an earlier paper[13] however, they reported that 616 pyelitis cases showed only 10.6 per cent with hemolytic B. coli but 73.2 per cent of these were females. In a more recent study Hill, *et al.*,[14] found that of 200 Gram-negative bacilli isolated from cases of genito-urinary infection 65.5 per cent were hemolytic.

Tinozzi[9] agreed with Schmidt in considering hemolytic properties of the colon group unrelated to their virulence, for among strongly hemolytic strains one finds those with slight virulence. On the other hand he states that hemolytic strains are more highly agglutinable than the non-hemolytic and the most virulent strains are also the most agglutinable. Dudgeon, *et al.*,[3] have suggested that the

hemolytic variety is especially liable to escape from the intestine into the blood stream whether directly or by way of the lymphatics.

Dudgeon, *et al.*,[3] in their carefully conducted study of the serological relationships among B. coli demonstrated that the hemolytic strains exhibit a far greater degree of homogeneity than do the non-hemolytic. They also have greater antigenic (agglutinin producing) properties than the non-hemolytic. This conclusion has received confirmation in the work of Meyer and Löwenberg[6] and of Löwenberg.[10]

In Dudgeon's paper published in 1926, and previously referred to,[4] he states "In my experience, when an abundant growth of hemolytic colon bacilli is obtained from the feces, there is a general toxemia, together with symptoms relevant to the intestinal tract, which may be controlled by specific hemolytic colon bacillary vaccines. This line of treatment in my hands has given better results than I have obtained with vaccine therapy in any other form of intestinal infection. Dudgeon, Wordley and Bawtree have also drawn attention to this fact, and considerable experience has led me to believe that this view is correct. The diarrhea and toxemia may subside, although resistant to other forms of treatment, and certainly vaccine therapy should be employed when these organisms are isolated from the feces and the clinical condition demands it. Patients with this form of intestinal infection may show the presence of specific agglutinins in the blood."

In an experimental study on dogs one of us with Rahe[15] in 1920 reported that it was possible through the use of autogenous vaccines to effect at least a temporary suppression of corresponding strains of B. coli naturally vegetating in the intestinal tract. The B. coli type employed in the vaccine was an autogenous sucrose-positive strain (B. coli communior). Its hemolytic capacity was not tested. A large dosage was used and a coincidence in the rise of the specific agglutinins in the blood with a decrease in numbers of the homologous B. coli strain in the stools was noted. As these B. coli were merely vegetating in the intestine the result was surprising and seemed to offer a rational basis for attempting to suppress or eliminate by autogenous vaccination more or less definitely parasitized B. coli as they occur in the abnormal human gastro-intestinal tract. Since then it has been established to our satisfaction that the same result may be attained with humans. In fact employing a hemolytic type of B. coli, which apparently has superior antibody stimulating properties, in the vaccine, a moderate and gradually increased dosage will often within a few weeks effect what is apparently a lasting elimination of that particular strain from the intestinal flora.

Our interest in the clinical significance of B. coli hemolyticus began in 1926 and since then we have examined a large number of fecal specimens. It is our purpose to present the results of our

findings, and to record our observations on the effect of treatment with autogenous vaccines, and with diets.

We have recognized as hemolytic B. coli only those strains producing a distinct zone of clearing beside the line of surface growth on blood (rabbit) agar. This zone, which may be narrow or broad, is evident within 5 hours' incubation.

The occurrence of B. coli hemolyticus in stools was found by one of us (J. C. T.) as in Table 1.

TABLE 1.—THE OCCURRENCE OF BACILLUS COLI HEMOLYTICUS.

Type.	No.	Positive.		Negative.	
		No.	Per cent.	No.	Per cent.
Normal adults	12	3	25	9	75
Adults with gastric anacidity	10	5	50	5	50
Psoriasis in adults	30	6	20	24	80
Cases with intestinal disorders, 96:					
Ulcerative colitis	41	23	56	18	44
Simple colitis	22	13	59	9	41
Intestinal toxemia	15	6	40	9	60
Dermatitis (mostly urticaria)	11	7	63	4	37
Diarrhea, spastic constipation or flatulence	7	7	100		

Totals, 96. Positive, 56 (58.4 per cent); negative, 40 (41.6 per cent)

Relative numbers of B. coli hemolyticus in positive specimens from among the preceding cases:

Total cases examined, 46

With 50 to 100 per cent hemolytic B. coli, 29 (63 per cent)

With less than 50 per cent hemolytic B. coli, 17 (37 per cent)

One of us (J. C. T.) has tested the comparative virulence of hemolytic B. coli and non-hemolytic B. coli. (Table 2.)

TABLE 2.—COMPARATIVE VIRULENCE.

Total strains tested, 102 (85 patients):

	Total.	Virulent.	Per cent.
Hemolytic B. coli	56	30	53.6
Non-hemolytic B. coli	46	11	23.9

These strains were isolated from patients exhibiting definite intestinal disabilities or symptoms referred to that tract. The virulence test was made by intraperitoneal inoculation of white mice.

In the laboratory of one of us (W. L. N.) there have been 672 fecal specimens examined from 458 patients. The feces from 161 patients were positive for hemolytic B. coli, an incidence of 31 per cent. Dr. Phebe L. DuBois has examined 343 fecal specimens from 219 patients of one of us and two colleagues. She found 161 positive specimens, an incidence of 32 per cent of patients. None of these patients were in normal health and they presented a great variety of diseases.

For the purposes of this study we have taken the clinical records of 180 patients, all private cases, who showed hemolytic B. coli in their stools on two or more examinations.

TABLE 3.—PATIENTS SHOWING HEMOLYTIC B. COLI IN STOOLS.

Simple colitis with intestinal toxemia	67
Ulcerative colitis	6
Urticaria	11
Angioneurotic edema	5
Acne (simplex and vulgaris)	16
Acne rosacea	5
Eczema	5
Pruritus	4
Fibrositis	7
Pyelitis	5
Chronic infectious arthritis	4
Psychoneurosis	7
Chronic duodenal obstruction	4
Peptic ulcer	5
Hypertensive cardiovascular disease	9
Epilepsy	3
Miscellaneous	17
Total	180

Of these patient 88 have been treated with autogenous vaccines and the results will be given in subsequent tables. The specific treatment was completed in all previous to March 1, 1932. The results have been ascertained since January 1, 1933, and stools from many have been examined recently.

The method of vaccination has been to give subcutaneous injections of the autogenous vaccine at intervals of 1 week. As many patients are extremely sensitive to the vaccine we begin with very small doses, —0.05 cc. which is equivalent to 50 million organisms, and increase 50 to 100 million according to the absence or presence of reactions. Local reactions are frequent and mild general reactions are not uncommon, while occasionally the local and general reactions are both quite severe. The average maximum dose is 600 million and we have never had occasion to exceed 1,000 million.

Believing that intestinal stasis tends to promote the growth of all organisms, we try to overcome it by mechanical means such as diet, mineral oil and agar. We have, however, seldom observed the disappearance of hemolytic B. coli by such means alone. The fecal specimens have been classified as putrefactive, semiputrefactive or fermentative in accordance with Tsuchiya's[16] classification. About 75 per cent of the stools containing hemolytic B. coli fall in the putrefactive or semiputrefactive groups. We have often been successful in transforming the flora to a fermentative type by diet and sugar but in no instance have the hemolytic B. coli disappeared by this treatment alone. In fact vaccination is the only method which we have found that eliminates the organisms. This has been successful in 93 per cent of our cases and the hemolytic B. coli have recurred in only 3 per cent of our patients whose feces have been re-examined after 1 or more years.

The results of treatment in several groups of patients are shown in Table 4.

TABLE 4.

	No.	Treated with vaccine.	Cured.	Unimproved.	Remarks.
Simple colitis with intestinal toxemia	67	30	25	0	No hemolytic B. coli in stools within 8 weeks in all but 5; of these, 3 showed very few; 1 recurred after 1 year with return of symptoms; 7 treated with diet, etc., but no vaccine; hemolytic B. coli present in large numbers in all after 4 months or longer.
Ulcerative colitis	6	6	4	1	1 patient apparently cured but relapsed after 1 year with return of hemolytic B. coli in stools; again improved with vaccine.
Urticaria—severe, chronic, recurrent	11	9	9	0	No hemolytic B. coli in stools within 8 weeks in all but 1; no recurrence in 2 years but hemolytic B. coli present in stools.
Angioneurotic edema	5	5	5	0	All were cured within 12 weeks; none relapsed.
Acne—severe and chronic	16	14	10	0	All greatly improved but results doubtful as local treatment also was usually given.
Acne rosacea	5	5	5	0	No recurrence.
Eczema	5	5	5	0	No recurrence.
Pruritus	4	4	0	4	No improvement in any, but hemolytic B. coli disappeared from stools in all within 12 weeks.
Fibrositis	7	5	5	0	All had symptoms of intestinal toxemia; no recurrences.
Pyelitis	5	5	5	0	All had hemolytic B. coli in stools and urine; no symptoms for over 2 years and in none has hemolytic B. coli recurred in stools.

Summary. 1. Strains of B. coli possessing hemolytic properties are frequently isolated from human feces (31 to 45 per cent of stools). They are somewhat more often found and in larger numbers in feces from patients with disorders relating to the digestive tract.

2. There is no distinctive difference either as regards morphology or cultural characteristics in the hemolytic B. coli strains isolated from the stools of normal or sick people, although those from the former group have seldom exhibited any virulence.

3. We have been successful in relieving the symptoms of toxemia by autogenous vaccines. B. coli hemolyticus has thus been eliminated from the feces in 93 per cent of our cases. They have recurred in 3 per cent after 1 year or longer.

4. Vaccination is the only method for eliminating B. coli hemolyticus from the human feces which we have found effective.

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THE FORMATION OF A HEMATOPOIETIC SUBSTANCE IN CONCENTRATED HUMAN GASTRIC JUICE.

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The therapeutic effectiveness of the parenteral injection of very small amounts of liver extract in the treatment of pernicious anemia was demonstrated by Gänsslen,[1] and Castle and Taylor.[2] Ederle, Kriech, and Gänsslen[3] also showed that an extract of hog gastric mucosa, when injected daily in small amounts, was effective in the treatment of pernicious anemia. Following this work and the fundamental work of Castle and his associates,[4] Morris, *et al.*[5] found that, although small amounts of normal human gastric juice were ineffective when injected intramuscularly, large amounts of normal human gastric juice or hog gastric contents after concentration *in vacuo* produced maximal reticulocyte responses when injected into patients with pernicious anemia. They described the substance in the concentrated gastric juice as being thermolabile, dialyzable, and exhaustible, and therefore concluded that it is probably a hormone. Conner[6] recently reported similar results in one case of pernicious anemia following the injection of normal human gastric juice after vacuum distillation. Wilkinson[7] was unable to confirm

the findings of Morris and his associates when he injected human gastric juice that had been brought to pH 7.5 previous to its concentration *in vacuo*.

In attempting to determine whether it was possible to separate the "active principle" in the gastric juice from the known enzymes (pepsin and rennin) we decided to subject human gastric juice to ultrafiltration. This procedure not only offered a means of determining the relative size of the various constituents of the gastric juice, but also offered a possible method of concentrating the gastric juice at ice-box temperatures.

Methods. All of the patients who received the concentrated gastric juice by injection were clinically and hematologically typical of pernicious anemia. Red blood cell counts, hemoglobin determinations (Newcomer), and reticulocyte counts were made daily during the test periods. The gastric juice used was obtained from young, healthy adults following the injection of 0.5 mg. of histamin subcutaneously. Immediately after collection, the gastric juice was filtered through No. 1117½ Falten filter (Carl Schleicher and Schüll). The number of milligrams of pepsin and rennin per cubic centimeter of the gastric juice to be concentrated was determined by methods described previously.[8]

The ultrafilters used in these experiments were of the Bechold type described by Bronfenbrenner.[9] An 8 per cent solution of soluble cotton in glacial acetic acid was deposited under pressure on the inner surface of a Norton alundum thimble. The pressure was applied for 1 minute and the solution was allowed to drain for 3 minutes before hardening.

Since the process of ultrafiltration required approximately 48 hours, the procedure was carried on in the ice box. The vacuum was produced by a water pump capable of reducing the pressure to 15 mm. of mercury. The gastric juice (285 to 630 cc.) was concentrated to a volume of 20 to 30 cc. and then diluted to 200 to 250 cc. with distilled water or 0.3 per cent HCl and reconcentrated to wash out as much of the filterable material as possible. This procedure was carried out twice before the gastric juice was reduced to its final volume of 13 to 15 cc. It was found that only negligible amounts of pepsin and rennin passed through such filters. By determining the amounts of these known enzymes in the ultrafiltrate (the portion of the fluid that passed through the filters), each new filter could be tested for possible defects in its construction.

To test whether the "active principle" of liver extract would pass through this type of ultrafilter, 1 patient with pernicious anemia received intravenously the amount of Liver Extract No. 343 derived from 100 grams of liver after the liver extract had passed through the ultrafilter. The patient's red blood count on the day of injection was 1.6 million, hemoglobin 48.4 per cent, and reticulocytes 0.3 per cent. Five days later a reticulocyte peak of 25.6 per cent (absolute reticulocyte count 620,000 per c.mm.) was reached. This maximal reticulocyte response was followed by marked clinical and hematologic improvement of the patient. This showed conclusively that the active principle in liver extract readily passed through the ultrafilter.

In those experiments in which concentration by vacuum distillation was employed, the procedure was as follows: The distilling flask (fitted with the usual capillary tube to prevent bumping) was immersed in a constant temperature bath maintained at 40° C. The vacuum was produced by a water pump. The gastric juice (500 to 600 cc.) was concentrated to 10 to 15 cc. in a period of from 3 to 5 hours.

Results. *I. Normal human gastric juice that had been stored in the ice box for 2 months.* The gastric juice used in the two following tests had been filtered through paper and then stored in the ice box for approximately 2 months. Following this the juice was subjected to ultrafiltration. The data for these experiments can be found in Table 1.

The concentrated juice (that held back by the 8 per cent membrane and which contained the enzymes pepsin and rennin), after being adjusted to pH 7 and passed through an "N" Berkefeld filter and injected into Case 1, produced on two occasions slight but definite reticulocyte rises (8 per cent and 10.2 per cent when the initial red blood counts were 1.38 and 1.60 million, respectively). Slight rises in temperature were the only evidence of reaction following the injections. There was clinical improvement following each injection, but the increases in red blood cells were not sustained and the patient had a further rise in reticulocytes (10.7 per cent) following the administration of Extralin.* The ultrafiltrate (the portion of the gastric juice passing through the ultrafilter) of this gastric juice was concentrated by vacuum distillation at 40° C., brought to pH 7, and passed through an "N" Berkefeld filter. The juice was then injected into Case 2*a* (Table 1). There was no reaction, no rise in reticulocytes, and no improvement in the clinical condition of the patient.

The two reticulocyte responses obtained were not maximal; therefore it was assumed that the storage in the ice box had possibly destroyed some of the active material.

II. Fresh normal human gastric juice. In this group of experiments the gastric juice was collected as described above, filtered through paper, and immediately ultrafiltered. The properties of the gastric juice, the red blood cell counts, and the hemoglobin and reticulocyte percentages of the patients following the injections are shown in Table 2.

The concentrates of the fresh human gastric juice were injected twice into Case 2 and once into Case 4. No reactions followed the two injections into Case 2 and no response of the blood or improvement in the clinical condition of the patient occurred until the patient received Extralin by mouth. Case 4 had a slight chill and a rise in temperature up to 102° F. following the injection, but there was no improvement in the patient during the 20 days following the injection. A reticulocyte peak of 48.5 per cent then followed the intravenous injection of the amount of liver extract derived from 100 grams of whole liver. Case 3 received the ultrafiltrate of the gastric juice injected into Case 2*b* after it had been concentrated by vacuum distillation, neutralized, and sterilized by passing through an "N" Berkefeld filter. There was no reaction and no

* A potent preparation obtained by the interaction of liver or liver extract with hog gastric tissue.

rise in the reticulocytes during the 14 days following the injection. This patient had previously responded to Liver Extract No. 343, but subsequently developed bronchopneumonia and died before again responding to the liver extract. Except for the first injection of the concentrate into Case 2 and the ultrafiltrate injected into Case 3, the materials injected were sterilized by the addition of tricresol. All subsequent preparations were so sterilized.

TABLE 1.—DATA CONCERNING USE OF GASTRIC JUICE STORED IN ICE BOX FOR APPROXIMATELY 2 MONTHS.

Case number	1 (*a*)			1 (*b*)			2 (*a*)		
Cc. gastric juice	350			500			500		
Original juice contained	Pepsin 4.44 mg. Rennin 45 mg.			Pepsin 3.13 mg. Rennin 27 mg.			Pepsin 3.13 mg. Rennin 27 mg.		
Part injected	Concentrate			Concentrate			Ultrafiltrate		
Ultrafiltrate contained	Pepsin 0 Rennin 0.8 mg.			Pepsin 0.02 mg. Rennin 0.12 mg.			Pepsin 0.02 mg. Rennin 0.12 mg.		
Day.	R. B. C. (cc.)	Hgb. (%)*	Retics. (%)	R. B. C. (cc.)	Hgb. (%)	Retics. (%)	R. B. C. (cc.)	Hgb. (%)	Retics. (%)
	1.38	34.4	0.1	1.60	37.8	1.2	2.06	44.0	0.1
1	1.21	31.3	0.6	1.40	34.4	1.4	1.81	52.1	0.2
2	1.17	29.3	0.3	1.66	37.7	1.1	1.99	49.7	0.1
3	1.40	38.5	0.4	1.59	34.4	1.0	1.85	49.7	0.1
4	1.47	....	0.9	1.36	37.7	2.4	1.45	47.8	0.2
5	1.41	32.7	1.9	1.45	34.4	1.4	1.94	47.8	0.1
6	1.42	36.2	5.6	....	....	2.1	....	....	0.2
7	2.07	38.2	8.0	....	....	4.7	1.99	48.0	0.2
8	1.67	38.2	3.0	1.59	37.0	3.5	2.20	45.8	0.1
9	1.35	35.8	4.0	1.69	37.3	8.8	1.64	44.4	0.0
10	1.58	36.8	2.1	1.42	40.9	10.2	1.55	39.3	0.2
11	....	....	1.2	1.50	39.1	6.3	1.46	35.4	0.3
12	1.60	37.8	1.2	1.65	37.3	4.4	1.43	36.2	0.4
13	....	....	....	....	....	2.3			
14	....	....	....	1.54	36.2	1.9			

Subsequent medication	Extralin 12 capsules daily		
	1.30	31.5	1.7
1	1.58	36.6	1.1
3	1.70	32.1	2.8
4	1.37	32.1	3.5
5	1.59	39.1	3.5
6	1.59	....	4.3
7	1.45	38.2	5.7
8	1.40	40.4	6.6
9	1.40	40.5	10.7
10	1.67	39.2	7.0
11	1.61	46.7	10.7
12	1.52	50.0	7.3
13	....	....	2.9
14	1.81	55.5	3.3
	1.85	53.7	3.7

* Newcomer method.

The results in this group of observations and those in the preceding group indicated that, although the fresh juice was inactive, the gastric juice that had been stored in the ice box for 2 months contained a demonstrable amount of a substance causing a reticulocytosis when injected into patients with pernicious anemia in relapse. However, Morris and his associates had obtained greater responses of the reticulocytes by the use of similar amounts of

TABLE 2.—DATA CONCERNING USE OF FRESH NORMAL GASTRIC JUICE.

Case number	2 (*b*)			3			2 (*c*)			4		
Cc. gastric juice	500			500			520			285		
Original juice contained	Pepsin 5.7 mg. Rennin 49 mg.			Pepsin 5.7 mg. Rennin 49 mg.			Pepsin 2.7 mg. Rennin 25.5 mg.			Pepsin 5.21 mg. Rennin 60 mg.		
Part injected	Concentrate			Ultrafiltrate			Concentrate			Concentrate		
Ultrafiltrate contained	Pepsin 0.1 mg. Rennin 0			Pepsin 0.1 mg. Rennin 0			Pepsin 0.05 mg. Rennin 0.23 mg.			Pepsin 0.0 Rennin 0.21 mg.		
Day.	R. B. C. (cc.)	Hgb. (%)*	Retics. (%)	R. B. C. (cc.)	Hgb. (%)	Retics. (%)	R. B. C. (cc.)	Hgb. (%)	Retics. (%)	R. B. C. (cc.)	Hgb. (%)	Retics. (%)
	2.05	45.8	0.3	1.49	26.3	0.3	2.26	55.5	0.2	1.49	35.1	0.0
1	2.08	47.8	0.3	1.30	28.5	0.2	2.20	45.8	0.2	1.49	30.4	0.0
2	....	....	0.3	....	....	1.4	....	....	0.1	1.40	33.7	0.1
3	2.11	43.0	0.1	1.33	26.3	1.4	2.04	49.1	0.1	1.30	38.2	0.0
4	2.02	40.0	0.9	1.16	26.1	0.6	2.03	47.8	0.1	....	....	0.0
5	2.10	46.2	1.2	1.10	27.3	0.3	2.26	51.3	0.0	1.18	26.6	0.0
6	2.21	50.0	1.2	1.44	27.3	0.6	2.16	55.5	0.0	1.39	31.2	0.8
7	2.25	44.1	0.9	1.38	23.9	0.4	2.25	45.8	0.0	1.25	30.7	0.0
8	2.04	....	1.5	1.20	....	0.6	2.11	44.7	0.5	1.36	26.4	0.0
9	....	....	0.6	....	....	0.1	....	....	0.1	1.39	27.7	0.0
10	2.08	46.2	0.9	0.88	25.4	0.5	....	....	0.1	1.11	26.0	0.1
11	2.02	47.8	1.0	1.03	22.7	0.3	1.95	45.8	....	....	....	0.2
12	2.00	49.1	0.7	0.85	20.8	0.3	....	....	....	1.39	28.3	0.0
13	1.82	50.0	0.3	0.78	18.3	0.1	....	....	....	1.30	25.6	0.0
14	....	....	....	....	....	....	....	....	....	1.17	24.2	0.2
Subsequent medication							Extralin 12 capsules daily			20 cc. L. E. No. 343 intravenously		
1							1.95	45.8	....	0.70	14.2	0.1
2							2.27	50.6	0.2	0.61	13.3	0.2
3							2.10	42.8	0.1	0.73	....	0.0
4							2.06	40.8	....	0.55	12.3	0.6
5							2.03	45.8	0.4	0.79	17.2	7.3
6							....	....	0.8	0.85	22.6	24.5
7							2.15	54.5	4.0	1.08	24.8	48.5
8							2.24	55.5	7.1	1.52	27.9	25.1
9							2.19	50.6	12.4	1.37	26.6	13.6
10							2.52	49.1	9.4	....	....	11.4
11							2.74	52.9	5.5	1.40	26.0	6.0
12							3.06	52.9	9.9	1.56	29.0	6.7
13							....	....	1.9	1.69	32.3	14.7
14							2.86	62.1	2.9	1.79	30.9	15.3
							3.31	63.7	0.6	1.96	37.8	13.4

* Newcomer method.

human gastric juice concentrated by vacuum distillation. This indicated that the process of vacuum distillation and, to a less extent, storage in the ice box for 2 months caused some change in the properties of the gastric juice resulting in a hematopoietically active substance.

III. Normal human gastric juice concentrated by vacuum distillation. In the first of these tests Case 6 was injected with the gastric juice concentrated by vacuum distillation only. A reticulocyte peak of 11.2 per cent and a satisfactory rise in red blood cells followed the injection. There was no further rise in reticulocytes following the administration of Extralin. In the remainder of the studies in this group the gastric juice was concentrated by vacuum distillation, diluted with distilled water, and then subjected to ultrafiltration. The various preparations were neutralized and then sterilized by the addition of tricresol before being injected into the patients. The properties of the gastric juice and the responses of the blood of the patients are shown in Table 3.

The portions of the gastric juice reconcentrated by the ultrafilters were injected on 4 occasions. A definite reticulocyte response followed each injection. Case 5 had a reticulocyte rise of 9.8 per cent by the 12th day after the injection. The reticulocytes decreased and the patient received Extralin by mouth. A reticulocyte peak of 27.9 per cent was reached 7 days later. The two responses were identical with the responses obtained in Case 11, except that Case 11 received no medication other than the gastric juice injection. Perhaps the second rise in this experiment was due in part to the gastric juice. The reticulocyte peak of 8.7 per cent (red blood cell count 3.25 million) in Case 8 was reached on the 13th day following the injection. There was no subsequent rise in reticulocytes following the intramuscular injection of liver extract. A reticulocyte peak of 8.2 per cent was reached by the 16th day in Case 10. A second reticulocytosis (9 per cent) followed the intramuscular injection of liver extract in this patient. Case 11 also received the reconcentrated gastric juice after he had responded to an injection of the ultrafiltrate. This second injection caused a slight (2.8 per cent) reticulocytosis and a further rise in red blood cells.

The ultrafiltrate of the juice concentrated by vacuum distillation was reconcentrated by vacuum distillation and injected into 2 patients. Case 7, a patient who had had nine previous responses to liver extract administered by mouth or by injection, was in cardiac failure when injected with the concentrated ultrafiltrate. By the 7th day the reticulocytes had started to increase, but the cardiac failure did not respond to therapy and the patient developed a bronchopneumonia and died on that day. Following the injection of the reconcentrated ultrafiltered gastric juice into Case 11 the reticulocytes increased to 8.2 per cent by the 9th day. After decreasing to 2.2 per cent they again increased, reaching 30.6 per cent by

* Newcomer method.

TABLE 3.—DATA CONCERNING USE OF GASTRIC JUICE CONCENTRATE

Case number	6			5			7		
Cc. gastric juice	560			425			560		
Original juice contained	Pepsin 3.9 mg. Rennin 41 mg.			Pepsin 2.9 mg. Rennin 37.5 mg.			Pepsin 2.9 mg. Rennin 37 mg.		
Part injected	All			Concentrate			Ultrafiltrate		
Ultrafiltrate contained	Pepsin — Rennin —			Pepsin — Rennin —			Pepsin — Rennin —		
Day.	R. B. C. (cc.)	Hgb. (%)*	Retics. (%)	R. B. C. (cc.)	Hgb. (%)	Retics. (%)	R. B. C. (cc.)	Hgb. (%)	Retics. (%)
	1.27	....	1.1	0.87	22.2	1.3	1.69	35.1	1.6
1	1.26	29.1	1.6	1.03	19.5	2.0	....	....	1.5
2	1.36	30.1	2.2	0.80	....	1.3	1.39	27.5	1.2
3	1.15	24.9	1.9	0.56	16.0	1.9	1.47	33.4	1.3
4	1.29	26.9	2.6	0.70	....	3.1	1.53	26.2	1.6
5	1.30	29.7	5.0	0.64	17.0	1.6	1.20	22.9	0.6
6	....	....	6.2	0.79	19.5	2.9	1.50	20.7	1.5
7	1.41	30.5	2.6	0.95	18.5	3.1	1.42	20.9	2.3
8	1.50	29.0	5.0	0.84	18.1	5.5	....	....	2.3
9	1.51	31.1	5.7	0.82	19.0	6.7	1.21	24.9	3.1
10	1.65	31.8	11.5	0.70	....	9.8	....	....	....
11	1.76	33.7	10.9	0.72	20.0	6.0	....	....	....
12	1.82	35.8	11.2	0.74	19.7	4.3	....	....	....
13	....	....	7.1	0.85	19.5	3.2	....	....	....
14	1.98	41.4	2.5	....	....	....	....	....	....
15	1.90	45.2	1.1	....	....	....	....	....	....
16	2.10	36.2	3.3	....	....	....	....	....	....
17	2.36	41.0	4.6	....	....	....	....	....	....
18	....	....	....	....	....	....	....	....	....
19	....	....	....	....	....	....	....	....	....
20	....	....	....	....	....	....	....	....	....
21	....	....	....	....	....	....	....	....	....
22	....	....	....	....	....	....	....	....	....
23	....	....	....	....	....	....	....	....	....
24	....	....	....	....	....	....	....	....	....
25	....	....	....	....	....	....	....	....	....
26	....	....	....	....	....	....	....	....	....
27	....	....	....	....	....	....	....	....	....
28	....	....	....	....	....	....	....	....	....
29	....	....	....	....	....	....	....	....	....
Subsequent medication	Extralin 12 capsules daily			Extralin 12 capsules daily					
	2.28	44.6	3.4	0.81	18.1	2.4	....	....	....
1	2.24	44.1	2.0	0.76	20.4	4.6	....	....	....
2	2.49	46.2	1.8	0.80	19.9	7.5	....	....	....
3	2.88	54.5	1.0	....	....	7.0	....	....	....
4	2.78	56.4	0.4	0.96	20.9	10.7	....	....	....
5	3.18	59.3	....	0.90	21.0	21.9	....	....	....
6	3.50	56.4	2.2	0.97	22.3	27.6	....	....	....
7	3.48	57.0	0.7	1.25	24.3	27.9	....	....	....
8	3.55	61.4	0.7	1.35	25.3	25.2	....	....	....
9	3.25	58.3	....	1.41	26.0	12.2	....	....	....
10	3.34	57.0	....	....	....	10.6	....	....	....
11	3.66	59.3	0.5	1.59	26.3	7.8	....	....	....
12	3.75	55.5	0.4	1.73	30.5	6.2	....	....	....
13	....	....	....	1.64	31.1	5.4	....	....	....
14	....	....	....	1.84	30.8	4.5	....	....	....

* Newcomer method.

BY VACUUM DISTILLATION AND THEN ULTRAFILTERED.

8			10			11			11		
560			518			518			630		
Pepsin 2.9 mg. Rennin 37 mg.			Pepsin 2.1 mg. Rennin 32 mg.			Pepsin 2.1 mg. Rennin 32 mg.			Pepsin 2.5 mg. Rennin 39.5 mg.		
Concentrate			Concentrate			Ultrafiltrate			Concentrate		
Pepsin — Rennin —			Pepsin 0 Rennin 0.07 mg.			Pepsin 0 Rennin 0.07 mg.			Pepsin 0 Rennin 0.006 mg.		
R. B. C. (cc.)	Hgb. (%)	Retics. (%)	R. B. C. (cc.)	Hgb. (%)	Retics. (%)	R. B. C. (cc.)	Hgb. (%)	Retics. (%)	R. B. C. (cc.)	Hgb. (%)	Retics. (%)
2.66	72.4	5.1	2.18	50.6	4.5	1.33	31.0	0.7	2.26	41.8	0.3
2.52	62.1	5.9	2.01	46.0	4.3	0.95	27.2	0.8	....	....	2.0
....	....	5.9	1.94	43.0	2.8	1.01	23.0	0.6	2.40	44.6	2.0
2.55	49.9	5.8	1.96	44.1	1.4	0.94	22.4	0.9	2.58	47.8	1.3
2.31	47.8	3.9	2.09	46.2	1.1	1.18	22.4	0.8	2.32	50.6	1.3
2.56	47.1	3.4	1.83	43.0	0.5	0.99	23.4	1.7	2.40	47.1	0.3
2.99	33.0	2.1	....	....	0.8	0.97	....	1.7	2.72	44.2	0.3
2.88	52.1	2.5	2.11	47.1	0.4	0.97	24.9	2.5	2.51	47.8	0.1
3.09	54.5	4.3	1.99	42.5	1.6	1.03	....	3.6	....	....	0.2
....	....	6.6	2.11	50.6	1.2	1.01	22.0	8.2	2.65	47.1	0.1
2.95	55.5	4.9	1.85	49.1	1.5	0.93	26.0	7.1	2.32	47.8	0.5
3.28	59.0	4.9	1.94	47.1	2.2	0.96	24.1	7.0	2.49	42.0	
2.61	55.5	6.7	1.95	50.5	1.9	1.10	25.2	4.7	2.69	47.1	1.7
....	....	8.7	....	....	1.6	....	....	2.2	2.70	54.7	2.8
3.25	64.9	6.5	....	....	3.1	....	....	4.1	2.44	50.6	0.9
3.21	62.1	6.9	1.60	50.1	4.1	1.22	29.4	3.6	....	....	1.3
....	....	4.8	1.91	....	8.2	0.87	25.2	7.8	3.30	50.6	1.6
3.26	64.9	3.1	2.38	55.5	5.3	0.82	....	10.6	3.28	56.4	0.9
			2.39	47.8	4.6	1.18	27.6	13.8	3.04	61.4	1.0
			2.66	52.1	3.2	1.46	35.3	20.0	3.24	59.8	
			....	....	3.0	....	....	26.2	3.30	59.3	
			....	....	1.8	1.75	....	30.6	3.44		
			2.50	48.4	1.4	1.71	35.4	16.1			
			2.40	57.0	1.0	1.67	35.0	11.0			
			2.43	57.0	0.8	2.12	41.6	2.3			
			2.38	51.3	1.2	2.26	41.8	0.3			
			2.29	53.5	1.1						
			....	....	2.6						
			2.56	44.6	0.8						
			2.39	48.4	0.9						
20 cc. L. E. No. 343 intramuscularly			20 cc. L. E. No. 343 intramuscularly								
3.64	68.1	3.8	2.39	48.4	0.9						
3.33	66.1	3.5	2.20	50.6	1.5						
3.77	66.1	1.0	2.08	47.8	1.3						
3.23	68.8	....	2.05	47.8	1.3						
3.79	62.5	1.7	2.27	53.0	4.0						
3.77	70.2	2.5	....	....	9.4						
....	....	....	2.70	54.5	9.0						
....	....	....	2.69	53.5	6.2						
....	....	....	2.62	59.3	3.2						
....	....	....	2.46	54.5	3.9						
....	....	....	3.14	56.4							
....	....	....	3.01	52.1	3.6						

the 21st day. At the onset of the second reticulocytosis there was an increase in nucleated red blood cells, nuclear particles, and myelocytes. In each of the experiments in this group the clinical response of the patient was proportionate to the height of the reticulocyte response. There was some type of reaction following each injection, and the most severe reaction occurred following the injection (Case 11, first injection) which caused the greatest reticulocytosis.

The fact that a definite reticulocyte response followed each injection of the gastric juice concentrated by vacuum distillation corroborated our hypothesis, made at the beginning of this group of observations, that the process of concentration by vacuum distillation produced some changes in the gastric juice. In Group II, however, the ultrafiltrate of fresh normal human gastric juice had been concentrated by vacuum distillation and no hematopoietic activity had been demonstrated in this concentrated juice; therefore it was assumed that the material in the gastric juice that could be made active by vacuum distillation was held back by the ultrafilters. To test this, the next observation was made.

IV. Fresh normal human gastric juice concentrated by ultrafiltration, diluted with 0.3 per cent hydrochloric acid, and reconcentrated by vacuum distillation. (See Case 12, Chart I.) Fresh normal human gastric juice (615 cc.) was concentrated by ultrafiltration. The concentrate was washed and then diluted with 0.3 per cent hydrochloric acid to 600 cc. and concentrated by vacuum distillation to 20 cc. The reconcentrated juice was neutralized and sterilized and injected intramuscularly into Case 12. The patient had a severe chill followed by a rise in temperature to 105.8° F. and was ill for 3 days. Within 36 hours the red blood cell count had dropped from 1.52 to 1.09 million, the hemoglobin from 36.2 to 26.5 per cent, and reticulocytes from 3 to 2 per cent, and there was a slight increase in icterus. The reticulocytes reached 10.5 per cent on the 10th day. After decreasing to 4.5 per cent, they again increased. At the beginning of this second rise there was a definite increase of nucleated red blood cells, nuclear particles, and myelocytes. The patient maintained an absolute reticulocyte count between 200,000 and 345,000 for 16 days. After 35 days the red blood cell count was 2.35 million, the hemoglobin 47.8 per cent, and reticulocytes 14.7 per cent. The absolute reticulocyte count on that day was 345,000, which was the peak of the reticulocytosis. By then there had been a definite clinical improvement and a definite increase in the red blood cell count, but the response was not as great as would be expected following the marked reticulocytosis. The patient was still slightly icteric. This response was atypical, as compared with those obtained with liver therapy. A subsequent rise in reticulocytes (15.3 per cent) followed the intramuscular injection of liver extract.

This study showed conclusively that the material in gastric juice which could be made active was held back by the ultrafilters used. It also demonstrated that the gastric juice concentrated by ultrafiltration and reconcentrated by vacuum distillation was hematopoietically active, whereas, on three occasions (Group II), gastric juice concentrated by ultrafiltration only had been inactive. The results obtained in Cases 10 and 11 and those obtained in Case 12 indicated that, after the concentration by vacuum distillation, a goodly percentage of the activity passed through the ultrafilters, although practically all of the material that could be made active by concentration by vacuum distillation was held back by the ultrafilters. It would seem, therefore, that during the process of vacuum distillation a hematopoietically active substance was obtained which was smaller in size than the material from which it was formed, or released.

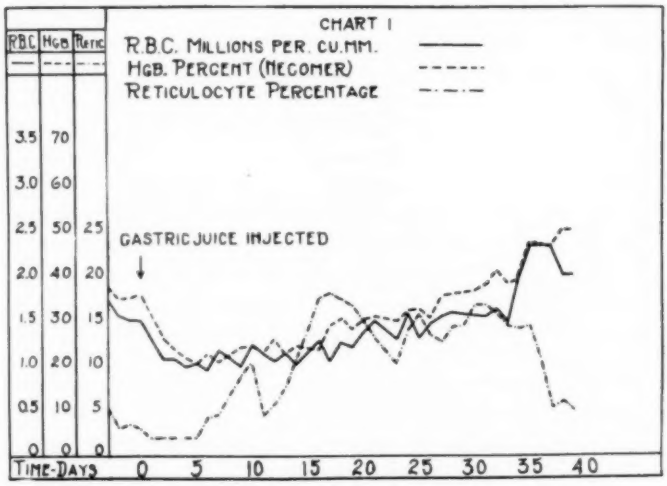

CHART I.

Discussion. In attempting to separate the material designated by Morris and his associates as "Addisin" from the known enzymes pepsin and rennin by the process of ultrafiltration, it was found that this could not be done except after concentration by vacuum distillation. Moreover, during the series of observations it became evident that some change in the fresh gastric juice must have taken place before a hematopoietically active material could be demonstrated.

That a change must have taken place was demonstrated when it was found that fresh human gastric juice after concentration by ultrafiltration was inactive; whereas, active preparations were

obtained when gastric juice that had been stored in the ice box for 2 months was concentrated by ultrafiltration and when fresh gastric juice was first concentrated by vacuum distillation. It was more conclusively shown when the concentrate of normal human gastric juice after ultrafiltration—which had been shown to be inactive on 3 occasions—was reconcentrated by vacuum distillation and was found to be quite active. The apparent change in the size of the active material also indicated that some change had taken place.

The actual mechanisms involved in this change are unknown. Three of the possible mechanisms are here presented:

1. *The action of the "intrinsic factor of Castle" upon an extrinsic factor present in the gastric juice.* Castle and his associates have demonstrated the presence of an "intrinsic factor" which when incubated with beef, beef muscle protein and yeast produces a material which will cause reticulocyte responses when fed by mouth to patients with pernicious anemia. It has recently been shown[10] that the incubation of Liver Extract No. 343 with normal human gastric juice markedly increases the potency of the liver extract. This is probably due to the action of the intrinsic factor of the gastric juice upon material in liver extract similar to that in beef muscle and yeast. We now have information, which will be published in detail at a later date, showing that the ultrafiltrate of fresh normal human gastric juice when incubated with Liver Extract No. 343 does not increase the potency of the liver extract, although the portion of the gastric juice concentrated by ultrafiltration does increase its potency. Therefore, it is evident that the portion of the gastric juice which when concentrated by vacuum distillation produces a material hematologically active when injected into patients with pernicious anemia, also contained the intrinsic factor of Castle previous to concentration by vacuum distillation. Moreover, the portion (the ultrafiltrate) which is inactive when concentrated by vacuum distillation does not contain the "intrinsic factor of Castle." The temperature at which vacuum distillation was carried out also offered ample opportunity for the intrinsic factor to act.

It seems reasonable to assume that hog gastric contents contain both the intrinsic and extrinsic factors, because of the presence of gastric juice, desquamated gastric cells, and partially digested food. Therefore the results reported by Morris and his associates, when they injected the concentrated gastric contents of cattle and hogs, could be explained by the action of the intrinsic factor, known to be present, on the extrinsic factor. Although it has been shown that the intrinsic factor is present in human gastric juice produced by histamin stimulation, the presence of the extrinsic factor has not been demonstrated. It is known, however, that gastric juice contains protein substances, and these substances could act as the extrinsic factor. The vitamin B_2 content of human gastric juice

is now being studied. If the extrinsic factor is present in the human gastric juice, some explanation must be made for the failure[4,10] of normal human gastric juice after 4 hours' incubation at 40° C. to produce reticulocyte responses when fed by mouth. At least two reasons suggest themselves. (1) The amount of extrinsic factor is so small that the quantity of the product is inadequate when fed by mouth; (2) in the gastric juice the extrinsic factor is in such a state that more active treatment than incubation at 40° C. is necessary before it can be acted upon by the intrinsic factor. That the intrinsic factor does not act upon the extrinsic factor of the muscle at the site of the injection has been suggested by the fact that the pathologic examination of animals, injected by Morris and his associates and by us, failed to reveal any signs of destruction, and proved by the fact that fresh gastric juice concentrated by ultrafiltration only (containing all the known gastric enzymes and the intrinsic factor) did not produce reticulocyte responses when injected into patients with pernicious anemia.

2. *Production of toxic material which produces the reticulocyte response by bone-marrow damage or by blood destruction.*

Phenylhydrazin, known to destroy red blood cells, is likewise known to produce a long sustained reticulocytosis in patients with polycythemia vera and in animals which receive this medication.[11] As pointed out by Morris and his associates, there is at the time of the reticulocytosis evidence of marked bone-marrow stimulation, that is, increase in nucleated red blood cells, nuclear particles, and myelocytes. Also, the type of the course taken by the reticulocytes is not the same as that seen after liver extract is administered by mouth or by injection. In our experience and in that of Conner, in contrast to the results reported by Morris, the reticulocyte response is delayed. It is also greatly prolonged and sustained, and the rise in red blood cells and hemoglobin percentage is also delayed. This is decidedly not the case when adequate amounts of liver extract are given by mouth or by injection. Delayed responses have, however, been reported when patients received large amounts of gastric tissue by mouth.[12]

In all the studies in which a reticulocyte rise followed the injection of the concentrated gastric juice, the patients had some type of reaction after the injection. The patients who had the greatest reticulocyte responses also had the most severe reactions. However, in some of our studies in which no response of the blood followed the injection, and in the one observation of Wilkinson, the patients experienced more or less severe reactions. Morris and his associates, however, have been able to eliminate the reactions following the injections by means of acetone extraction of the concentrated gastric juice. Even if the reactions are not always associated with reticulocyte rises, the type of reticulocyte response resulting from these injections still suggests that it may be due to bone-marrow irritation

or to actual blood destruction. The fact that concentration by vacuum distillation produces an acidity of the gastric juice approximately equivalent to that of 2 normal hydrochloric acid indicates that considerable hydrolysis, with resulting protein degradation products, might take place. Such protein degradation products could be quite irritating to the bone marrow or could actually be destructive to the red blood cells with the resulting bone-marrow stimulation. Case 12 is of interest in this connection. There was an actual decrease of 0.55 million red blood cells following the injection, and this decrease was accompanied by an increase in icterus. There was no definite increase in the red blood cells of this patient until after a prolonged reticulocytosis. Faber[13] in 1922 reported evidences of bone-marrow stimulation and occasionally rises in red blood cells and hemoglobin following the injection of sterilized milk into patients with pernicious anemia. The responses did not always follow the injections, however. No reticulocyte counts were recorded.

3. *Activation of a gastric hormone.* If the substance in normal human gastric juice, concentrated by vacuum distillation, which produces reticulocyte responses when injected into patients with pernicious anemia, is a hormone, our work demonstrates that the hormone must be activated by concentration by vacuum distillation, or by standing in the ice box for at least 2 months before it will produce a reticulocytosis. The results of our studies confirm the findings of Morris and his associates with regard to the fact that a hematopoietically active substance can be demonstrated in gastric juice concentrated by vacuum distillation when injected into patients with pernicious anemia in relapse. The prolonged reticulocytosis and the evidence of marked bone-marrow stimulation were likewise observed by us. However, we were unable to demonstrate the presence of a hematopoietically active material in human gastric juice until some change in the gastric juice had occurred. It is our opinion, therefore, that the hematopoietic substance must be formed by the action of the intrinsic factor on an extrinsic factor, or by the production of a substance irritating or toxic to the hematopoietic system.

Summary. 1. By the methods employed it was found impossible to separate the enzymes, pepsin and rennin, from the hematopoietic substance in human gastric juice except after concentration of the gastric juice by vacuum distillation.

2. The process of concentration by vacuum distillation or storage in the ice box for 2 months was necessary before the presence of a substance capable of producing a reticulocyte response when injected into patients with pernicious anemia could be demonstrated.

3. The possible mechanisms involved in this change in the gastric juice have been presented.

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STUDIES ON THE PHYSIOLOGY OF THE PARATHYROID GLANDS. IV. RENAL COMPLICATIONS OF HYPERPARATHYROIDISM.

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Simple hyperparathyroidism is now a well understood disease. Its cardinal metabolic abnormalities are hypercalcinemia, hypophosphatemia, hypercalcinuria and hyperphosphaturia. Its usual clinical import centers around the symptoms arising from the accompanying skeletal decalcification and dephosphatization. The present paper is concerned with the types of renal complication which may be associated with hyperparathyroidism, and the case history and metabolic findings in a patient with one of these types are set on record.

It is probable that the kidney may be involved in hyperparathyroidism in three entirely different ways, here referred to as Types I, II and III. These are arranged in order of the severity of the hyperparathyroidism with which they are apt to be associated. It

will be easier to discuss Type III before Type II. The essential features of the types are as follows:

Type I. Pyelonephritis secondary to formation of calcium phosphate stones in renal pelves.

Type III. Acute parathyroid poisoning with anuria, and death from undetermined cause in a few days, with calcium deposits in kidney parenchyma as well as in other organs, but with no chronic renal changes.

Type II. A condition midway between these two, which simulates both chronic glomerular and vascular nephritis. It differs from Type I in that the deposits are in the kidney parenchyma rather than in the kidney pelves, and from Type III in that the kidneys show long-standing changes and may be the only organs involved in the calcium deposits.

Type I Variety of Renal Involvement in Hyperparathyroidism. The formation of renal calculi in hyperparathyroidism with resulting pyelitis and pyelonephritis has been so much emphasized by all writers on the subject that it requires little discussion. The sequence of events is very simple. The calcium and phosphorus excretions in the urine are much increased in this disease; this predisposes to the formation of stones; the subsequent course is that of recurring renal stones. Among the first case reports of renal calculi in typical hyperparathyroidism were the 2 cases reported by Stenholm in 1924.[1] In both instances the stones were bilateral. Mandl's original case,[2] the first one diagnosed as hyperparathyroidism, excreted a white sediment in his urine as did the first patient, C. M., studied in this clinic,[3] although neither showed renal calculi by Roentgen ray. C. M., however, subsequently did show renal calculi as well as evidence of Type II renal involvement (*v. infra*). Other cases to show renal calculi were those of Harbitz, 1915;[4] Hoffheinz, 1925;[5] Wanke, 1926;[6] Parreira and Castro-Freire, 1926;[7] Barr, Bulger and Dixon, 1929;[8] Leri, *et al.*, 1930;[9] Hunter, 1931;[10] Cosin, 1931;[11] Weil, *et al.*, 1931;[12] Hunter, 1931—3 additional cases;[13] Fraser, 1931—3 cases (quoted by Hunter[13]); Albright, Bauer, Claflin and Cockrill, 1932;[14]* Noble, 1932,[15] and 3 unpublished cases from this clinic. Thus actual renal stones occurred in 23 proven cases. This is an incidence of 27 per cent in the series of cases which the writers have analyzed. This series included 74 cases from the literature, 7 unreported cases from this clinic, an unreported case from the Johns Hopkins Hospital Clinic, and a new case reported in this paper, making a total of 83 cases, 10 of whom have been studied in this clinic. This series does not include cases with histologic or chemical evidence of hyperparathyroidism when the tumor has not been found, nor cases with a parathyroid tumor but no histologic or chemical evidence of hyperparathyroidism. Renal stones should

* At the time this patient was reported no parathyroid adenoma had been found, but a subsequent operation revealed the tumor.

always bring up the question of an underlying hyperparathyroidism. The Urologic Service at this hospital recently has been doing routine serum calcium and phosphorus determinations on patients with renal stones, and at the time of writing has made the diagnosis of hyperparathyroidism 4 times where the diagnosis would never have been suspected otherwise. Only 2 of these have yet come to operation and in each patient a parathyroid adenoma was found.

Type III Variety of Renal Involvement in Hyperparathyroidism. Collip[16] showed that excessive doses of parathormone in dogs resulted in a few days in death, which was preceded by anuria and retention of nitrogenous products. Hueper[17] showed that such dogs dying from acute parathyroid poisoning, as it were, had calcium deposits in their thyroid glands, mucous membrane of the stomach, lungs and kidneys. There seems little doubt, therefore, that an excessive level of the parathyroid hormone in the blood in a few days can so alter the equilibrium that calcium in some form is deposited into the tissues mentioned and death ensues. The kidney lesions here are only a part of a more generalized process. The term "Type III variety of renal involvement" is used to designate the type of lesion seen in parathyroid poisoning.

From a clinical point of view the chief importance of this condition is its avoidance while parathormone is being used therapeutically. No instance of acute parathyroid poisoning from injection of the hormone has been reported. Many of the cases of hyperparathyroidism reported in the literature, however, are at about the critical level where one might expect the complication of parathyroid poisoning. It would be surprising if some did not transgress the level. It seems most likely that the patient reported by Dawson and Struthers[18] is a unique instance of acute parathyroid poisoning occurring in man due to a parathyroid tumor.

The patient, a 49-year-old laborer who, for several years, had had symptoms referable to his skeleton, "on the 24th of October was suddenly seized with a heart attack and was admitted to the hospital in the evening in a state of collapse with a very rapid and feeble pulse. He was too ill to give an account of himself and died suddenly the following morning without any precise conclusion as to the cause of the collapse having been arrived at." Autopsy revealed osteitis fibrosa cystica generalisata of von Recklinghausen. Except for the skull and humerus the disease was in an early stage. A parathyroid adenoma 1 inch in length was found. The internal organs showed no macroscopic changes. Microscopically, calcium deposits in the form of fine granules, which in some instances became confluent masses, were present in all the internal organs. Special sites of deposits were the internal elastic lamina of the arteries, heart wall, lungs, stomach and kidneys.

There seems almost no question but that this patient was suffering from hyperparathyroidism complicated by parathyroid poisoning

which caused a "chemical death." It would appear, therefore, that a condition analogous to parathyroid poisoning in dogs may occasionally occur in man. It must be emphasized that it is rare and that the diagnosis should be confined to cases showing a rapid exit—chemical death, as it were—calcium deposits in multiple tissues at postmortem, and absence of chronic changes in the kidneys.

Type II Variety of Renal Involvement in Hyperparathyroidism. There are many cases of hyperparathyroidism with renal lesions on record which do not fall into either Type I or Type III groups. In Type I it would appear that calculi are precipitated out from the urine as secreted by the kidney, thus forming stones in the kidney pelvis; in Type III the supposition is that calcium phosphate is precipitated out from the intercellular fluid into multiple organs, including the kidney; in Type II the evidence, we believe, suggests that the calcium phosphate is precipitated out of fluid in the tubules, forming concretions in the kidneys which eventually lead to inflammatory changes, sclerosis and contracted kidneys.

Of our series of 83 cases, 17 taken from the literature show evidence of chronic parenchymatous kidney pathology. This high incidence shows that there must be some causal relationship. The descriptions of the kidneys in the individual cases seem consistent with the sequence of events suggested above. These descriptions are given below (*q. v.*).

We had the opportunity to study recently a patient who has typical Type II renal involvement, and the metabolic studies threw further light on this condition.

Case Abstract. Patient C. E. S. (M. G. H. No. 320037), a white girl, aged 13, entered this hospital on March 17, 1932, having been referred by Dr. A. S. Merrill of Manchester, N. H., because of the Roentgen ray findings. She is the youngest patient with hyperparathyroidism in the series, there being only 3 other cases under 20 years (Cosin,[19] aged 17; Cooley,[20] aged 14, and Pemberton and Geddie,[21] aged 14). Her chief complaint was bone trouble of 2 years' duration. Her first symptom was a slight limp in the left leg associated with slight stiffness of the left knee. This knee gradually began to rotate inward a little, and 1.5 years before admission was operated upon for a cyst and a portion of the bone was removed. Five months before entry the right knee began to catch when she stepped on it in a certain way, causing sharp pains, but never preventing her from fully extending her leg. Otherwise the child was able to be up and about and to play a little with other children. Her appetite was good although she had lost 6 pounds during the previous 6 months. During the past 3 to 4 years she had been troubled with enuresis and nocturia (2–3×). She urinated 6 to 10 times during the day and drank 12 and 13 glasses of water. On a fixed water intake of 2000 cc. on the ward she was constantly thirsty. Her dietary history was not remarkable.

Past History. She had an unexplained rash at 18 months, whooping cough at 8 years, measles at 11, and only 2 or 3 "sore throats" during her entire life. Her tonsils and adenoids were removed at 7 years. She sustained a fracture of the right forearm at 9 years, as a result of adequate trauma. Catamenia began at 11 years.

Physical Examination. A rather flabby, pale, little girl, normally developed for her age, and very intelligent. Her gait had a peculiar wobbling character, suggesting relaxation of joint ligaments together with marked hypotonia. There was a valgus deformity of the right knee. At least 20 purpuric spots up to 2.5 cm. in diameter were present on her extremities. The retinal arteries showed rather marked variation in caliber. The blood pressure was 150/80. The heart was enlarged to the left, 1 cm. beyond the midclavicular line. The apex impulse was forceful and there was an apical systolic murmur.

Laboratory Examinations. Urine: Specific gravity during a concentration test varied only between 1.002 and 1.005; albumin, strongly positive; sediment, many white cells without casts. Red count, 4,300,000; hemoglobin, 80 per cent; white count, 8900. Blood smear normal except for slight achromia; Hinton test, negative; basal metabolism, +4; phenolsulphonephthalein intravenous renal function test, 15 minutes, 1 per cent excretion; 30 minutes, 4 per cent excretion; 90 minutes, 10 per cent excretion. Blood non-protein nitrogen, 55 and 66 mg. per 100 cc.; serum carbon dioxid combining-power, 44.4 volumes per cent; serum protein, 6.5 per cent; serum calcium, 12 mg. per 100 cc.; serum inorganic phosphorus, 4.7 mg. per 100 cc; plasma phosphatase, 36 units (method of Bodansky[22] where normal is about 3 units).

Roentgen Rays. "All the vertebræ of the spine show a distinct variation from the normal. Changes are most marked in the lumbar and lower dorsal region and consist of a disturbance of normal trabeculæ. Denser areas are just below the intervertebral disks, midportions of the vertebræ being more radiant." "The long bones, skull, and pelvis are also grossly abnormal. Most marked changes are at the epiphyses where almost complete decalcification or acalcification is present and considerable interference in growth has taken place. Decalcification extends, however, to involve the shafts and flat bones. There are changes suggesting partial displacement of epiphyses and periosteal reaction. The skull and pelvis present finely granular appearance with some increase in width in bone and miliary areas of decalcification and increased calcium deposit. Bones of the pelvis show what appear to be definite cystic areas. No other cystic areas are seen in any of the long bones. The ribs on the left side, left femur, and distal epiphyses of radius and ulna show a marked deformity. The appearance in the skull and pelvis is almost identical with osteitis fibrosis cystica and hyperparathyroidism. Changes in the epiphyses, periosteum and vertebræ are rather unusual." (Drs. G. W. Holmes and A. O. Hampton.)

Diagnosis. The polyuria, polydipsia, decalcification with cyst formation, and hypercalcinemia seemed consistent with hyperparathyroidism. The absence of hypophosphatemia was against this diagnosis, but it was thought that this might be ascribed to the renal involvement. Renal insufficiency there was in any event, but the question was whether this was secondary to a hyperparathyroidism or whether the renal condition was primary and the skeletal changes represented renal rickets, the exact nature of which is still somewhat problematical (*v. infra*). Metabolic studies were made, but were not helpful in making a diagnosis, since they were not typical of uncomplicated hyperparathyroidism. This lack of confirming evidence of hyperparathyroidism we had to discount, however, in view of the renal impairment, the modifying effect of which on the metabolic findings in hyperparathyroidism had never been studied. It was decided that the only hope rested on the diagnosis being hyperparathyroidism, and the patient was explored. A biopsy on the right iliac crest was first performed, however, to rule out multiple myeloma. A parathyroid tumor (22 by 17 by 10 mm.) was found on operation and removed.

Biopsy Report. Osteitis fibrosa cystica.

Pathologic Report. The gland is typical parathyroid tissue. The cells with the exception of one circumscribed area are the rose-red type of chief cell. There is, however, a circumscribed area, not separated from the rest of the gland by any connective tissue septum, in which the cells are larger and lighter (see "plant-cell-like chief cell;" see also "Wucherungsherde," Erdheim[23]). Welch cells are absent. No colloid is seen. There is a lace-work structure of connective tissue which divides the whole gland into small acini.

Course in Hospital. The evening of the operation (April 9) she developed tingling in the fingers, and by the next morning she had a positive Chvostek sign. On April 12 she developed mild carpopedal spasm and a positive Trousseau sign (serum calcium = 7.5 mg. per 100 cc.). She was discharged from the hospital on June 16, 1932. At that time there had been no demon-

TABLE 1.—METABOLIC DATA ON K.S. BEFORE AND AFTER REMOVAL OF PARATHYROID TUMOR.

Metabolic period.	Urine, cc.	Calcium, gm.				Phosphorus, gm.				Serum, mg. per 100 cc.		Plasma phosphatase, units.	Remarks.
		Urine.	Feces.	Intake.	Balance.	Urine.	Feces.	Intake.	Balance.	Ca.	P.		
I	4520	0.29	0.96	0.31	−0.94	1.18	0.96	1.74	−0.40	13.6 (II)*	4.3	36	Enuresis.
II	6000	0.27	0.64	0.31	−0.60	1.55	1.21	1.74	−1.02	13.6 (II)	4.2	..	Enuresis.
III	5920	0.29	0.64	0.31	−0.62	1.40	0.53	1.74	−0.19	12.6 (I)	4.4	37	Enuresis.
Blank 3-day period.	...	...	...	...	.....	...	...	...	.....	10.4 (I) 8.3 (II) 7.5 (III)	4.2 3.3 4.1	38	Operation (I).
Blank 3-day period	...	...	...	...	.....	...	...	...	.....	7.7 (I) 6.1 (II) 5.7 (III)	4.3 4.4 4.7		
Blank 3-day period	...	...	...	...	.....	...	...	..	.....	7.5 (I)	4.7		
Blank 3-day period	...	...	...	...	.....	...	...	...	.....	5.3 (I) 5.5 (III)	5.0 5.3		
IV	5945	0.08	0.48	0.28	−0.28	1.18	0.50	1.56	−0.12	6.5 (I)	6.4	..	Enuresis.
V	5710	0.06	0.32	0.31	−0.07	1.14	0.50	1.73	+0.09	6.0 (III)	6.2	..	Enuresis.
VI	5700	0.07	0.37	0.31	−0.13	1.14	0.62	1.74	−0.02	.....	..	..	Enuresis.
VII	5860	0.08	0.47	0.31	−0.24	1.10	0.77	1.74	−0.13	8.0 (III)	6.4		
VIII	5760	0.10	0.19	0.31	+0.02	1.02	0.21	1.74	+0.51	7.6 (III)	5.7		
IX	5390	0.08	0.57	0.31	−0.34	0.90	1.00	1.74	−0.16	.....	..	15 (III)	
X	5680	0.09	0.41	0.31	−0.19	0.90	0.80	1.74	+0.04				
XI	5530	0.08	0.59	0.31	−0.36	0.88	0.72	1.74	+0.14	8.0 (III)	5.7	19 (III)	

* Roman numerals indicate to which day of period—1st, 2d, 3d—notation refers.

strable change in her urinary findings, kidney function, or bone Roentgen rays. Her postoperative course was complicated only by a few episodes of vomiting and by mild attacks of carpopedal spasm, for which parathormone was administered on 4 occasions and calcium gluconate on 4 occasions.

Metabolic Findings. The metabolic data are contained in Table 1. They consist of calcium and phosphorus determinations on the urine and feces

during 16 3-day metabolic periods. The methods were those previously employed in this clinic.[24,25] Periods 1 to 3 were pre-operative; periods 4 to 11 were postoperative. Sufficient time (about 6 weeks) elapsed between periods 3 and 4 to allow the patient to recover from the immediate effects of the operation. The patient was on a neutral low-calcium diet during the entire experiment.

The calcium excretion in the urine during periods 1 to 3 is quite interesting. It averaged 283 mg. per 3-day period. This figure is to be compared with 190 mg., the average urinary calcium excretion for normal individuals on a similar régime,[25] and 1310 mg., the corresponding excretion of a patient with a hyperparathyroidism and a blood calcium of about 14 mg.[3] It will be seen that the high urinary calcium excretion usually seen in hyperparathyroidism is apparently much reduced in the presence of this renal complication. The average fecal calcium excretion per 3-day period was 744 mg., which is slightly higher than the figure of 600 mg. obtained for normals. The significance of this is increased by the fact that in hyperparathyroidism as a rule there is a decreased amount of calcium in the feces (see Albright, Bauer, Claflin, and Cockrill,[14] observation VII, p. 421). The net result was an average negative calcium balance of 722 mg. per period as compared with 460 mg. for the normals. In brief, this patient excreted less calcium in the urine and more in the feces than would have been predicted had she not had renal disease complicating the hyperparathyroidism. An examination of the phosphorus figures during periods 1 to 3 reveals very much the same thing. There was an average negative phosphorus balance of 537 mg. during these periods, but whereas in simple hyperparathyroidism the phosphorus excretion is almost entirely in the urine,[14] here 40 per cent of the excretion was in the feces. It seems apparent that the lack of hypophosphatemia in this patient was connected with this relative lack of phosphorus excretion by the kidney.

The findings during periods 4 to 11 are about what one would expect. The urinary calcium excretion was below that of normal, but not less than what one would expect for the degree of hypoparathyroidism present (serum calcium, 6 to 8 mg.); the fecal calcium excretion was about normal, which further emphasized the observation that it was increased during periods 1 to 3; the urinary phosphorus excretion in spite of the higher serum phosphorus was much reduced from the pre-operative figures with less reduction in the fecal phosphorus excretion, the ratio of fecal phosphorus to total remaining about 40 per cent (actually 38+ per cent).

The plasma phosphatase findings were interesting. They were very high and apparently stationary before the operation (36 units per 100 cc. 23 days before the operation and 37 units on the day of the operation). Two days after the operation the level was 38 units; 23 days after, the level had fallen to 24 units. The fall continued, and after 54 days a value of 19 units was obtained; 3 days later a value of 15 units; and 1 week later (64 days after operation) a value of 19 units. The normal value by the method employed[22] is about 3 units. These findings show pretty clearly that the hormone is not directly concerned in the production of the enzyme, but rather produces bone changes which in turn are associated with an enzyme increase. Normal enzyme levels are not to be expected until the bone changes have entirely retrogressed.

From the metabolic data the following conclusions are suggested:

I. Renal insufficiency complicating hyperparathyroidism may produce: (*a*) An absence of the characteristic finding of hypophosphatemia; (*b*) a reduction of the characteristic high partition of phosphorus excretion in the urine as compared with the feces, and

(*c*) a reduction of the characteristic hypercalcinuria and an increase of the characteristic decreased fecal calcium excretion.

II. The level of plasma phosphatase is not directly related to the parathyroid hormone, but is dependent on the bone changes.

*Metabolic Studies, on Previously Reported Case, Before and After Development of Renal Impairment.** The above observations are substantiated by similar studies on another patient. This second patient was the same sea captain, C. M., who had already been the subject of several investigations.[41,26,27,3,28] His story to this time was one of typical hyperparathyroidism in 1926; removal of 2 parathyroid glands which were normal or even hypoplastic in appearance; no subsequent change in his calcium and phosphorus metabolism (in spite of many quotations to the contrary in the literature); improvement with dietary measures; but renal impairment (Types I and II) during the past year. In spite of several attempts, no more parathyroid tissue had been found.† He was studied for 4 3-day periods on a low-calcium neutral diet, and it is of interest to compare these data with similar data obtained in 1926 before the development of the renal impairment. The average figures are shown in Table II. It will be observed that the observations noted above are substantiated.

In June, 1932, the following laboratory data of interest were obtained. The Roentgen ray of the kidneys showed, besides stones in the pelvis, "probable calcification in the region of the cortex of the right kidney" (Dr. A. O. Hampton). The urinary findings were albumin, moderately positive; sediment, many white blood cells with rare hyalin and granular casts. The blood non-protein nitrogen was 58 mg. per 100 cc.; the carbon dioxid combining-power of whole blood was 48.6 volumes per cent. Three months later the phenolsulphonephthalein excretion was 10 per cent in 2 hours after intramuscular injection.

Reported Cases of Hyperparathyroidism with Renal Lesions. I. *Askanazy.*[36] Interestingly enough this is the first case of hyperparathyroidism on record (1903). Abstract from autopsy: "Both kidneys are removable only with difficulty from their capsula fibrosa; are small and fairly soft; and have surfaces which are definitely granular. On the cut surface one sees homogeneous pale-red tissue with white calcium streaks in the pyramids."‡ Microscopically "the kidneys show the picture of interstitial nephritis with many small areas of calcification in the cortex and medulla."

II. *Molineus.*[37] Case 2. Woman, aged 59, with "contracted kidneys."

III. *Idem.* Case 3. Woman, aged 48, with "contracted kidneys."

IV. *Harbitz.*[4] Autopsy diagnosis: "Chronic interstitial nephritis, associated with pyelitis and calcareous concretion of phosphates and carbonates."

* The new metabolic data on this patient were furnished us by Dr. Walter Bauer, to whom we are much indebted.

† At a 7th operation a parathyroid tumor was removed from the anterior mediastinum. Death ensued several weeks later due to a complication.

‡ Translations are our own.

V. *Meyer*.[38] Microscopic findings. "In the cortex one sees many hyalinized degenerated glomeruli. Besides the fully hyalinized glomeruli one sees some with a concentric connective tissue capsule of a thickness varying up to total replacement of the glomerulus. The epithelium of the tubuli contorti for the most part is well stained. Here and there one finds, however, tubules with desquamated epithelium without nuclei. Fat is not demonstrable in the epithelium. The lumina of the tubules is often noticeably wide. There are no demonstrable changes in the vessel walls. Nevertheless, one finds in the vicinity of small vessels many fresh hemorrhages. Blood cells are often present in the lumina of the tubules. The connective tissue shows, especially in the region of more or less severely altered glomeruli, a marked degree of infiltration with round cells. In the middle of such infiltrations one sees flaky calcium concretions stained blue-black. Here and there it can be clearly seen that these calcium concrements are deposited on the tubular epithelium. In the medulla there are many calcium deposits also, sometimes surrounded by an area of inflammation, sometimes lying in the lumen of a tubule and causing no reaction. In the neighborhood of such calcium infarcts one sees many markedly dilated urinary tubules. Besides the inflammatory infiltration one finds, in the medulla as well as in the cortex, areas of fibrous connective tissue with few nuclei."

TABLE 2.—A COMPARISON OF THE CALCIUM AND PHOSPHORUS METABOLISM OF A PATIENT WITH HYPERPARATHYROIDISM BEFORE AND AFTER DEVELOPMENT OF RENAL IMPAIRMENT. THE FIGURES FOR NORMAL INDIVIDUALS ARE LIKEWISE INCLUDED FOR COMPARISON.

	Calcium, gm.					Phosphorus, gm.					Serum, mg. per 100 cc.	
	Output.			Intake.	Balance.	Output.			Intake.	Balance.	Ca.	P.
	Urine.	Feces.	Total.			Urine.	Feces.	Total.				
Control series†	0.13	0.32	0.45	0.33	−0.12	1.21	0.60	1.81	2.07	+0.26	10.0*	4.0
Average of 3 periods in 1926 before renal impairment[3]	1.31	0.19	1.50	0.31	−1.19	2.22	0.24	2.46	2.10	−0.36	14.0	2.7
Average of 4 periods in 1932 after renal impairment	0.27	0.79	1.06	0.30	−0.76	2.12	0.66	2.78	1.77	−1.01	14.4	4.2

* Serum values for control group are merely approximate.

† Average values calculated from Farquharson, Salter, Tibbetts and Aub[48] of 14 3-day periods on 4 normal individuals on a neutral low-calcium diet.

VI. *Hartwich*.[39] Anatomical diagnosis "nephrocirrhosis arteriosclerotica."

VII. *Parreira* and *Castro-Freire*.[7] "Calcareous concretions in the kidneys, renal pelves, and bladder."

VIII. *Wanke*.[6] "Granular contracted kidneys with marked calcium deposits in the calices."

IX. *Ask-Upmark*.[40] "There are considerable changes in the renal tissue with alteration of the smaller arteries as by arteriosclerosis, with a partly hyalin transformation of the glomeruli and with a noticeable atrophy of the convoluted tubules. There are, furthermore, numbers of calcium deposits situated in the distal parts of the tubular system (Scholtstucken and collecting tubules), in some places secondarily involving the interstitial tissue."

X. *Ask-Upmark*.[41] No history of chronic nephritis in this case. Kidneys were normal in size, but there were "in the cortex and especially in the pyramids several fine, yellowish, dry stripes of lime."

XI. *Bergstrand*.[42] A woman, aged 55, who had a high blood pressure on several occasions, although not consistently. The urine showed a trace of albumin and a specific gravity of 1.005 to 1.008. Autopsy: "The kidneys are somewhat diminished in size. The capsules are removed with difficulty. The surfaces are diffusely granular, reddish brown. The cortex is narrower than normal and of varying width." Microscopic examination: "In the kidneys the desquamated contents of the tubules as well as the hyalinized glomeruli show definite calcification of their media. Calcium deposits also occur interstitially. The calcification is most marked in the tips of the pyramids, where the deposits are macroscopically visible. Most of the glomeruli are completely or partly hyalinized. In others one sees capsular proliferation or increased number of cells in tubules. In a few places calcification in the outer leaf of Bowman's capsule was seen. The glomerular changes are consistent in every respect with those which one finds in nephrosclerosis."

XII. *Noble*.[15] Autopsy: Chinaman, aged 40. "The right kidney weighed 105 gm.; the cortex had an irregular gray area of scar tissue to which the capsule was adherent. The medulla and pelvis contained a few small calcified masses. Left kidney weighed 100 gm. and showed similar changes."

XIII. There can now be included in this series the patient with chronic nephritis and parathyroid tumor reported by *MacCallum*[43] in 1905, because a reëxamination of the bones of that patient showed increase in size of Haversian canals and fibrosis of the bone marrow with many osteoclasts.* The patient was a male, aged 26, who died in uremia after having suffered for several years with chronic nephritis and who showed at autopsy "chronic diffuse nephritis." It is of interest that this author wondered at the time if there was any relationship between the tumor and the nephritis, and even reported negative findings in the parathyroid glands in two other cases of chronic nephritis. This, we believe, was the first attempt to correlate chronic nephritis with parathyroid pathology.

We include in Type II, as a subgroup, 4 cases who died of chronic renal insufficiency and which showed at autopsy in addition to the chronic kidney lesions also calcium deposits in other soft tissues. We first included those cases under Type III, but it seemed more likely that the sequence was as follows: development of hyperparathyroidism, deposition of calcium in kidneys, development of renal insufficiency (Type II variety), retention of phosphates, and finally precipitation of calcium phosphate in other soft tissues as a terminal manifestation of chronic renal insufficiency—just as is sometimes seen in chronic nephritis without parathyroid disease (Schmidt[49]).

XIV. *Hoffheinz*, 1925.[5] Clinical diagnoses included that of "contracted kidneys." Non-protein nitrogen of blood was raised to 221 mg. with a blood pressure of only 85/55. The patient died in uremic coma. Autopsy: "Calcium metastases in the lungs; many calcium bodies and calcium infarcts in the kidneys. Besides a large coral-like stone filling the upper part of the right kidney pelvis, there were many small stones on both sides, the size of a pinhead to that of a lentil seed. Marked hydronephrotic dilatation of the right kidney pelvis with severe atrophy of the kidney tissue. Severe chronic hemopurulent pyelonephritis and cystitis with very marked areas of contraction in both kidneys (right kidney, 8.5 by 4 by 2.5 cm. in size, 85 gm. in weight; left kidney, 11 by 5.5 by 3 cm. in size, 120 gm. in weight)."

* Personal communication from Dr. W. G. MacCallum.

This case was, furthermore, remarkable in that all the parathyroids showed tumor formation (see also Cases 11, 16 and 17).

XV. *Peneche*, 1926.[44] Clin. diag.: Chronic nephritis. Autopsy: "Contracted kidneys with calcium retention therein and extensive calcium metastases in the body. These were found especially in the muscle of the left heart, in the neighborhood of the orifice, in the auricle and apex of the heart, in the arteries of the thyroid, kidneys and spleen. The large vessels remained free. Furthermore, there were calcium concretions in the point of the tongue, skin and in the wall of the parathyroid tumor. Microscopically there were calcium concretions demonstrable in the examined glands of internal secretion."

XVI. *MacCallum* (unreported case*). Johns Hopkins Hosp., No. 34560. Autopsy 11797. Male, aged 23. Symptoms (started in August, 1930): Nausea, weakness and vomiting; cleared after 1 week, but the patient never felt strong again. Polyuria and nocturia were noted. Blood pressure was 140/100. Red count was 2,500,000. The blood urea nitrogen was 185 mg. per 100 cc. The urine showed albumin, a few red and white cells. The specific gravity of the urine varied between 1.007 and 1.009. The patient died on January 12, 1931. No bone changes were found clinically. At autopsy there was extensive calcification of alveolar walls, bronchioles, and venules of lungs; lobular pneumonia; extreme chronic nephritis with calcification of tubules; hemorrhagic spots in stomach. Both lower parathyroids were enlarged (2 by 1.5 cm.). The bone of the vertebra was much rarefied; trabeculæ in many places were eroded and excavated by a fibrous marrow tissue with numerous large osteoclasts.

XVII. Finally, mention must be made of the case reported by *Hubbard* and *Wentworth*[45] which most nearly falls into Type II, but which has certain features which make it entirely unique.

Male, aged 20. Clin. diag.: Chronic nephritis. Roentgen rays showed extensive calcification of peripheral arteries and deposits of calcium about the joints. The blood calcium was elevated. Autopsy: "Severe interstitial nephritis with a right hydronephrosis, calcium deposits in the wall of the left auricle, extensive and marked calcification of the smaller peripheral arteries, the arteries of the gastro-epiploic omentum, and the jejunum, but sparing the liver, spleen, lungs, kidneys and stomach, and osteitis fibrosa particularly marked in the skull, ribs and vertebræ, and two large parathyroid bodies, 2 cm. in diameter. . . ." The location of the calcium deposits is unusual in this case, although very much the same as in the case reported by Peneche (*v. supra*).

Discussion. Most of the points which we wished to bring out have been discussed in the subject matter, but there are a few entirely unrelated aspects which require further discussion.

The diagnosis of hyperparathyroidism immediately suggests severe bone lesions. It is probable, however, that the degree of bone involvement is an index to the duration of the disease, not to its severity. Therefore, it is not surprising that our only case of parathyroid poisoning had only slight bone disease. A rapidly developing tumor could theoretically kill a person from parathyroid poisoning without there being any bone lesions. A case has recently been operated upon in this clinic, and a tumor removed, in whom

* Dr. W. G. MacCallum called this case to the attention of one of us and the notes were made directly from the hospital record and the autopsy protocol furnished by him.

there were no bone lesions by Roentgen ray and no elevation of blood phosphatase.

In English, in contrast to German, the term "nephritis" has been used for many conditions where no inflammation is thought to exist, and the term is almost synonymous with "renal insufficiency." If the same inaccurate nomenclature is to continue, "chronic parathyroid nephritis" might be applied to the Type II kidney lesions. The initial disturbance, however, is not an inflammation, but presumably a deposition of calcium. Therefore, the term chronic nephro-calcinosis would seem preferable. The same kidney lesions are found in other conditions, but the mechanism of their production is probably the same. (Thus patients with multiple myeloma often develop similar lesions [Perla and Hytner[29]].)

Under the general heading of prognosis and treatment, these are a few points which seem important. Obviously, one does not expect the sclerosed kidney of Type II to recover completely. The question is whether, once the cause has been removed, the condition will remain stationary in contrast to chronic glomerular nephritis or even show slight improvement. Our patient should answer this question in time. But preventive treatment is a real problem for the patient like C. M., who first enters with normal kidneys; on whom the parathyroid tumor is not found; and who later enters with impaired kidneys. Fluids should, of course, be forced in such a patient to keep the urine as dilute as possible. One might suggest giving ammonium chlorid to keep the urine acid, thus preventing deposits, but this is certainly contraindicated in view of the observation of Albright, Bauer, Ropes, and Aub,[30] that this drug very much enhances the decalcifying power of the parathyroid hormone. Furthermore, warning must be made that the two best indirect methods of combating the demineralization both increase the danger of kidney damage. Thus a very high-calcium diet may overcome the negative calcium balance, but this would tend to increase urinary calcium excretion. This tendency in the absence of renal damage is very slight, as shown by Bauer, Albright and Aub,[3] the urinary calcium of their patient with hyperparathyroidism being about the same whether the patient was on a high- or a low-calcium diet. Another theoretical danger of high-calcium diet in such a patient, however, is the possibility of producing parathyroid poisoning, just as so nearly happened in the patient of Hunter and Aub's,[31] when a low-calcium diet was changed to a high one, the dose of parathormone remaining constant. But more danger of renal involvement probably lies in the high-phosphorus diets suggested by Albright, Bauer, Claflin and Cockrill.[14] Such therapy is attended with a tremendous increase in phosphate excretion in the urine, coupled, to be sure, with a decreased calcium excretion. These authors warned against the possibility of kidney damage and suggested using sodium acid phosphate, so as to insure an

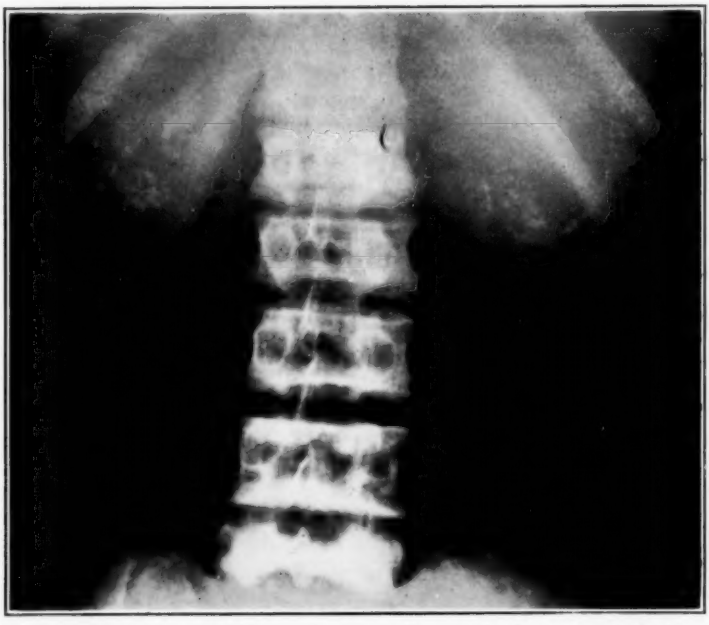

FIG. 1.—Roentgen ray of kidneys of case not discussed in this series who had hyperparathyroidism complicated by Type II kidney pathology. Calcium deposits can be seen to occur in collecting tubules, each pyramid being represented by a clump of calcium dots. This case was diagnosed and referred to us by Drs. Magendantz and Eddinger at the Boston Dispensary and will be reported in detail by them.

FIG. 3.—Roentgen ray of K. S. before operation, showing widening and irregularity of epiphyseal line.

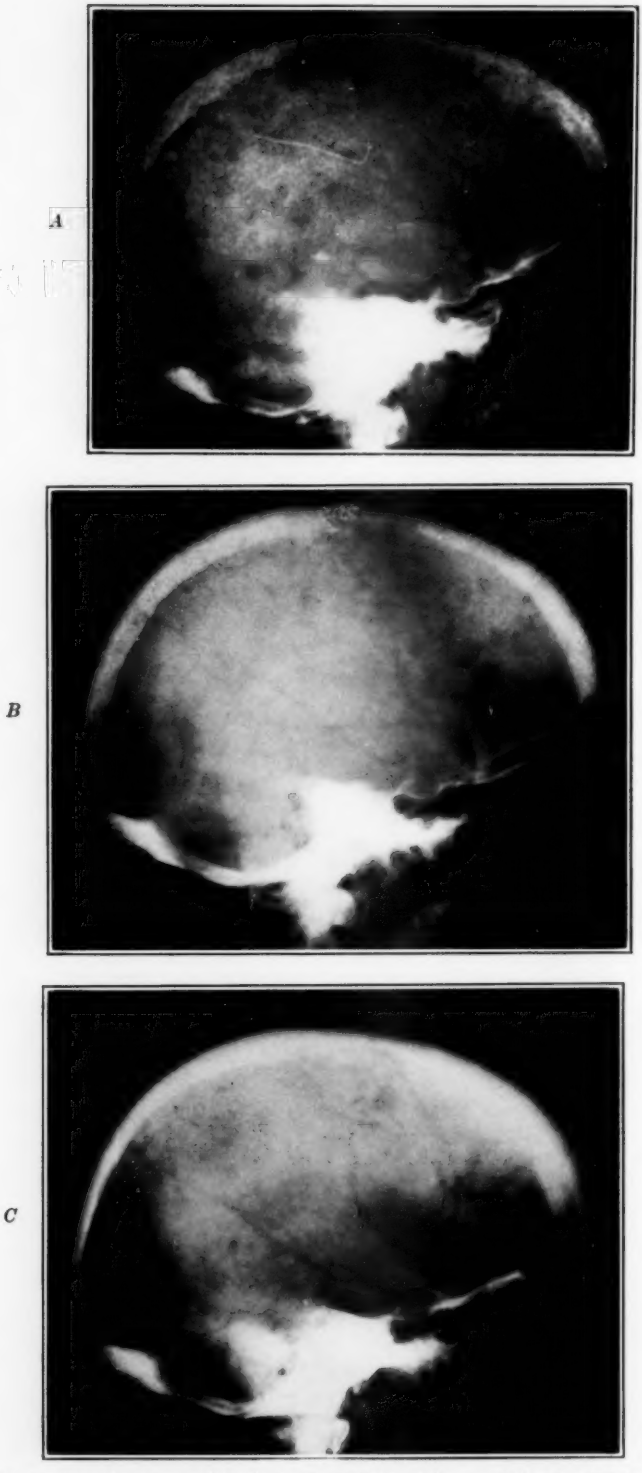

FIG. 2.—Roentgen rays of skull of patient N. B., taken on July 28, 1930, October 4, 1930 and September 20, 1932, showing that decalcification responds to dietary treatment alone (see text).

acid urine. In the present state of our knowledge it would seem wise, given a patient with hyperparathyroidism in whom surgery has failed to remove the cause, to follow very carefully the serum calcium and phosphorus values during the instigation of either a high-calcium or a high-phosphorus diet, and to make sure that there is no tendency to the changes associated with parathyroid poisoning. The development of both a high serum-calcium and a high serum-phosphorus value should be regarded as a danger signal of parathyroid poisoning.

A good case to illustrate the possibilities and limitations of medical treatment is the patient N. B., previously reported[14] in connection with some phosphate ingestion experiments. She, in short, was a married woman, aged 41, who entered the hospital in 1930 with typical osteitis fibrosa cystica, bilateral renal stones, and the metabolic findings of hyperparathyroidism. Because no tumor was found at operation an effort was made to combat her disease with medical methods. Except for a short period of a high-phosphate diet, a high-calcium diet was used. This régime succeeded in recalcifying her skeleton, as is demonstrated in Fig. 2, which shows a series of Roentgen ray plates of her skull. But a check-up examination in 1932 revealed that she had developed definite kidney damage, with fixation of specific gravity and reduced phenolsulphonephthalein excretion. A parathyroid adenoma was removed at a second operation (Cope). Thus it would appear that the skeletal disease can be improved by medical means, but that kidney damage continues. The only satisfactory therapy, therefore, is surgery and, above all, surgery by a person who has made a special study of the problem. This aspect, however, is so important that it requires special consideration in a more appropriate place.

Patient K. S. showed a marked disturbance in the calcification of the subepiphyseal region by Roentgen ray (Fig. 3), suggesting that the zone of provisional calcification in the growing cartilage was being inadequately calcified. This has not been a feature of experimental hyperparathyroidism in animals, and the epiphyseal lines in the girl aged 14, reported by Amberg[32] and later by Pemberton and Geddie,[21] were normal. However, the published Roentgen rays on the boy aged 14 reported by Cosin[19] show somewhat similar changes. No mention of the epiphyseal lines in the girl aged 14, reported by Cooley,[20] was made. But before acalcification is added to decalcification as a feature of hyperparathyroidism because of this finding in K. S., it must be realized that some complicating factor may be entering into this case. Thus the possibility exists that the hyperparathyroidism caused the kidney damage, but that this in turn caused the acalcification of the growing epiphyses.

The association of such lesions in the epiphyses, together with renal changes naturally brought up the question of the as yet inadequately explained condition, renal rickets. Such a diagnosis

certainly seemed to fit K. S. When the true nature of her condition was revealed by operation, the question arose whether all so-called cases of renal rickets are not hyperparathyroidism with Type II renal lesions. However, from Mitchell's[33] excellent review of the subject of renal rickets, it seems almost certain that chronic renal insufficiency will in itself lead to rachitic-like changes in the skeleton. It appears equally certain, however, that, in several instances in the past where renal rickets has been diagnosed, an underlying hyperparathyroidism almost surely was present. The evolution of symptoms, for instance, in many of the quoted cases suggested that the skeletal symptoms antedated the renal. Furthermore, the Roentgen ray changes in the skeleton, the pathologic changes in the bones, the refractiveness to vitamin D, and the frequency of urinary calculi in cases of renal rickets all suggest the possibility of hyperparathyroidism. The fragmentary reports which are available concerning the blood calcium level in so-called renal rickets are rather against the suggestion that it is frequently due to hyperparathyroidism. The blood calcium levels tend to be depressed rather than elevated. There are a few cases of hypercalcinemia, as the case with a level of 14.6 mg. reported by Parsons.[34] There is this to be said, however: We do not know whether an excessive amount of parathyroid hormone will maintain a high blood calcium in the presence of as severe phosphate retention as was present in most of the cases of renal rickets. It may be that just as hypophosphatemia is no longer a criterion of hyperparathyroidism in the presence of renal damage, so hypercalcinemia may likewise cease to exist under such conditions. Preliminary observations on patients with chronic nephritis suggest that parathormone will not elevate their blood calcium levels.* With this short survey, the subject must be left for further data. Certainly hyperparathyroidism with renal damage has masked under the name of renal rickets in some cases, but that all cases of renal rickets are so to be construed is highly improbable (see case with congenital cystic kidneys, etc.). Examination of the parathyroid glands at autopsy should settle the question in any one case. Mitchell's monograph gives no reference to such examination. Lathrope's case[35] showed normal parathyroid glands at autopsy.

One further possibility must be discussed. Could the changes in the parathyroid glands by any chance be secondary to the renal disease? This would only have to be considered in the few cases where multiple parathyroid glands were involved (*v. supra*—Cases XI, XIV, XVI, XVII). Since the parathyroid hormone raises blood calcium and lowers blood phosphorus, any influence opposing these actions might be attended by hyperplasia of the glands. A low-calcium intake, for example, causes hyperplasia.[46,47] It seems conceivable, therefore, that a chronic renal insufficiency with phosphate

* Unreported data (Albright and Ellsworth).

retention and a high inorganic phosphorus level might likewise cause hyperplasia of all parathyroid tissue which might go on to multiple tumor formation. As far as the writer is aware, of all the cases with hyperparathyroidism, only those with kidney damage have shown multiple tumors. In these cases the kidney damage may be the cause and not the result of the parathyroid tumors.

Summary and Conclusions. 1. In hyperparathyroidism, calcium phosphate precipitates may cause three types of renal impairment depending on the locus of precipitation, *viz.:* Type I, precipitation in renal pelvis with resulting pyelonephritis; Type II, precipitation in renal tubules with resulting renal sclerosis, contraction and insufficiency; Type III, precipitation in kidney as one of several organs with acute renal failure, and death of undetermined cause in a few hours or days.

2. A review of 83 cases of hyperparathyroidism revealed 23 patients (27 per cent) with Type I lesions, 19 patients (23 per cent) with Type II, and 1 with Type III.

3. It is pointed out that the presence of a renal stone should suggest the possibility of hyperparathyroidism, and 2 cases are cited where this one finding led to such a diagnosis and the removal of a parathyroid adenoma in each instance.

4. The renal lesions of hyperparathyroidism can occur without bone lesions, the former being an index to the severity of the disease, the latter an index to its duration.

5. Metabolic studies were done on 2 patients with Type II lesions and revealed certain differences from the findings in similar studies on patients with hyperparathyroidism but without renal involvement, *viz.:* (*a*) Hypophosphatemia was not present; (*b*) the degree of hypercalcinuria was decreased; (*c*) the fecal calcium excretion was increased rather than decreased; (*d*) the partition of phosphorus in the urine as compared with the feces was less elevated.

6. Patients with Type II lesions often present a clinical picture very similar to that of chronic glomerular nephritis, but the scarcity of casts in their urinary sediment is a helpful differential point. The term nephro-calcinosis is suggested for this type of kidney lesion.

7. Following parathyroidectomy, the blood phosphatase level only gradually returns to normal, suggesting that the parathyroid hormone is not directly responsible for the production of the enzyme. Patients with hyperparathyroidism and no bone changes may have normal plasma phosphatase levels. The plasma phosphatase level is probably an index to the amount of bone disease and is independent of the degree of hyperparathyroidism.

8. Lesions in the growing epiphyses as shown by Roentgen ray suggestive of rickets were present in the patient here reported, and the question is raised whether so-called renal rickets may not often be hyperparathyroidism before closure of epiphyses complicated by

the Type II renal lesions. The evidence is almost conclusive that such is not always the case.

9. Whereas hyperparathyroidism can cause parenchymatous kidney damage, 3 cases are cited from the literature in which parenchymatous kidney disease was associated with multiple parathyroid tumors, and the question is raised whether in these instances the parathyroid hyperplasia was not secondary to phosphate retention dependent on the renal insufficiency.

10. As regards prophylactic therapy for the prevention of renal damage in hyperparathyroidism, it is pointed out that fluids should be forced; that an alkaline urine should be avoided; that ammonium chlorid and presumably other acidosis producing salts are contraindicated; that a high-phosphorus diet, while indicated for the demineralization, imperils the kidneys and should be used only when the blood values can be carefully followed; and that the same applies to a high-calcium diet, although to a less extent.

11. A case of hyperparathyroidism is cited where medical treatment was followed by marked improvement of the bone condition, but where kidney damage eventually occurred; and the point of view is expressed that almost all patients with this disease will eventually develop kidney damage unless the condition is corrected by successful surgery.

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A PHOTOGRAPHIC SUSPENSION STABILITY (SEDIMENTATION RATE) APPARATUS.

(PRELIMINARY REPORT.)

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THE purpose of this paper is to describe a photographic recording instrument which it is felt will simplify and improve the sedimentation test, now so widely used.

The three principal methods for the determination of the sedimentation rate or suspension stability of blood are: I, *the time method*[1] in which the time required for the blood corpuscles to fall a certain distance is measured (*i. e.*, number of minutes required to fall 18 mm. in the Linzenmeier method); II, *the distance method* (2*a*, *b*, and *c*) in which the distance the blood corpuscles fall in a certain length of time is measured (*i. e.*, number of mm. at the end of 1 hour, 2 hours, or longer); III, *the graphic method* (2*c*) in which the distance of sedimentation of blood corpuscles is observed

continuously or at definite intervals for a given period of time (usually 1 hour).

Fåhraeus,[2] Cutler,[3] Rourke and Ernstene[4] and others have investigated the graphic method. The following are the advantages of this method as summarized from the above work: (1) A characteristic line or curve is obtained, *i. e.*, horizontal, diagonal, and vertical lines and curves. (2) the steepness of the curves may be interpreted in terms of the severity of the disease. A diagonal curve is of much more serious import than a horizontal curve. The vertical curve usually indicates very marked disturbance; (3) changes in the curves during the course of an illness seem to have some prognostic significance and serve as an index of the patient's progress; (4) the straight line period of constant sedimentation may be observed and the period of most rapid fall of blood corpuscles may be evaluated therefrom (Rourke and Ernstene); (5) the periods of "aggregation" and "packing" may be observed.

The graphic method is not commonly used because it is troublesome and time consuming. By the photographic technique, the advantages of the graphic method are retained and the following disadvantages are eliminated: (1) The observer is not required to make constant or frequently repeated observations for the period of 1 or more hours; (2) the maximum number of determinations an experienced observer can do at the same time by the graphic method is three. By the photographic method the number of determinations is only limited by the size of the apparatus used; (3) the personal equation of the observer which may introduce an error is eliminated.

The present status of the numerous methods for the determination of the sedimentation rate and the use of the hematocrit have been briefly summarized by Wintrobe[9] who states "A variety of instruments have been employed for the determination of sedimentation rate." The presentation of another instrument therefore requires some justification because the multiplicity of techniques has already led to confusion. A disadvantage of the instruments commonly employed is that they can be used only for the determination of sedimentation rate. The employment of the hematocrit for this purpose is of special value because it has been demonstrated by several observers[4,5] that anemia magnifies and polycythemia minimizes the actual rate of sedimentation of the blood. If sedimentation is measured in a hematocrit, the volume of the packed red cells may subsequently be determined without further trouble. In this way an accurate measure of the degree of anemia or polycythemia is obtained and an appropriate correction can be made. A correction chart which is applicable to the instrument here described (Wintrobe hematocrit) is supplied by Rourke and Ernstene.[4]

"The hematocrit is filled to the '10' or '0' mark. For the determination of sedimentation rate the fall in the upper level of red cells is measured in millimeters by the calibrations and numbers at the left of the scale. . . . There is considerable debate

whether the single observation of the distance which the red cells have fallen at the end of 1 hour is an adequate test of the suspension stability of the red corpuscles. The instrument described is, however, suitable for the 'time,' 'distance,' or 'graphic' procedures. . . ."

The Photographic Suspension Stability Apparatus here described employs the Wintrobe hematocrit. The above statements are, therefore, equally applicable to the photographic method.

The sedimentation procedure causes no loss of time in hematocrit determinations, since it is an advantage to allow the hematocrit to remain standing for 1 hour before centrifugation in order to permit settling of the colorless corpuscles and platelets in the uppermost layer of the hematocrit as pointed out by Wintrobe.[9]

General Principle and Description of Apparatus. The principle of the photographic suspension stability apparatus is based on the difference in density to light between plasma and plasma plus blood corpuscles in a glass vessel. The intensity of the light is adjusted so that plasma will transmit, while plasma plus blood corpuscles will not transmit light. When a tube containing blood to which an anticoagulant* has been added is allowed to stand, the height of the column of plasma will increase with time, while that of the blood corpuscles will decrease. When light, as above described, is projected upon such a tube, the plasma will transmit the light, while the portion of the column containing plasma plus blood corpuscles will not transmit light.

The blood-filled glass tubes are inserted in the walls of an octagon or square housing (serving as a camera). Within the housing is a kymograph drum propelled by a low speed clock mechanism. Light sensitive photographic paper is fastened to the drum. The paper is thus in constant motion and the light transmitted by the plasma makes a continuous record on the photographic paper. Upon completion of the determination, the photographic paper is removed, developed and fixed, thus presenting a permanent, accurate and continuous record of the suspension stability or "sedimentation" of the specimen of blood (Plates I and II).

Figures 1 and 2 are vertical and plan views of the apparatus. Figure 3 is a vertical view of one side of the housing. Figures 4 and 5 are vertical and plan views of the receptacles with the hematocrits in place.

Detailed Description of Apparatus. The housing consists of a "light-tight" wooden box surrounding the kymograph drum. This serves as a camera obscura. The inner surface of the center of each face (side) of the housing is at a distance of 2 mm. from the surface of the drum (Fig. 2). There are three receptacles (*R*) in each face of the housing and they are located in the approximate vertical centers of the faces (Fig. 3). These receptacles (*R*) are rectangular wooden blocks capable of receiving hematocrits filled with blood. They can be inserted in slots in the housing and may also be easily removed.

* For effect of different anticoagulants and quantity of anticoagulant on suspension stability, see Rourke and Plass.[6]

Figure 4 is a vertical view and Fig. 5 a horizontal section of the receptacle, 150 by 35 by 25 mm., with the hematocrit *in situ*. In the receptacle there is a bore 6.5 mm. in diameter and 123 mm. in height for the hematocrit. In the top of the receptacle and centered in same is a bore 28 mm. in diameter and 15 mm. deep. The latter bore accommodates the thumb, index finger, and hematocrit, enabling one to place the latter in the receptacle.

SI is a slit 1 mm. wide extending for a distance of 70 mm. below the level

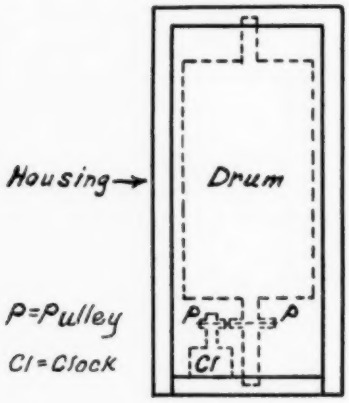


Fig. 1.

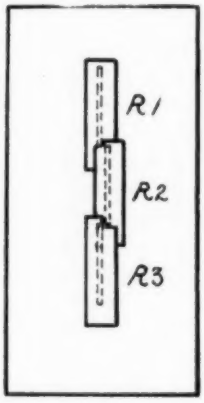


Fig. 2.

Figs. 1 and 2.—Vertical and plan views of the photographic suspension stability (sedimentation rate) apparatus.

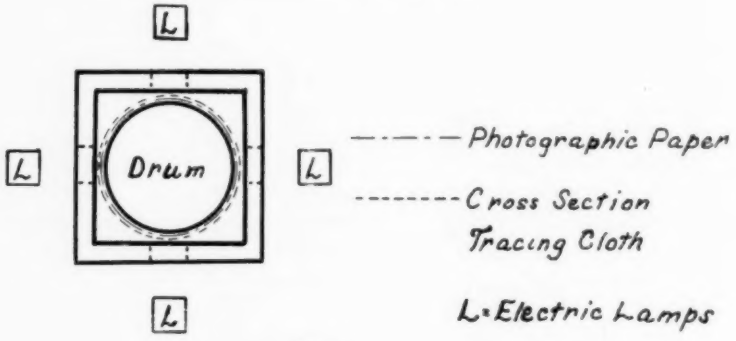


Fig. 2.

Fig. 3.—Vertical view of one side of the housing.

of the blood in the hematocrit (*i. e.*, the 100-mm. mark). The light from source (*L*) is projected upon the slit and thereby upon a narrow column of blood in the hematocrit. With the sedimentation of the blood corpuscles, the light transmitted affects the photographic paper. It is shown as the large black area in Plates I and II.

SII is a slit 1 mm. wide and 3 mm. long extending from 2 to 5 mm. above the level of the blood in the hematocrit. This slit constantly transmits a narrow beam of light and thereby indicates the start, duration and end of the experiment. The 3 mm. heavy upper line in Plates I and II is the result

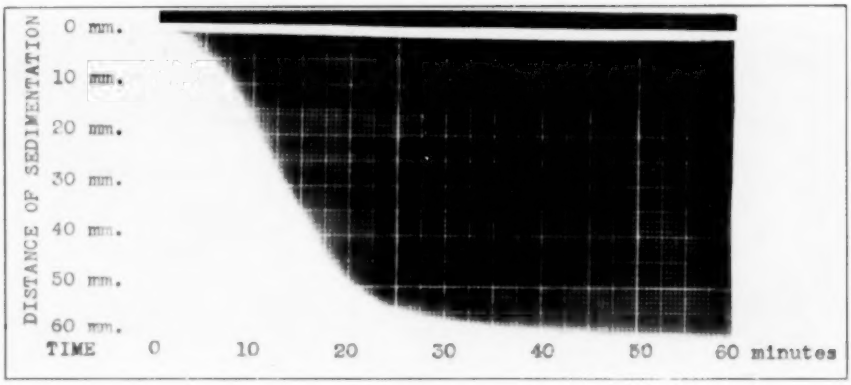


PLATE I.

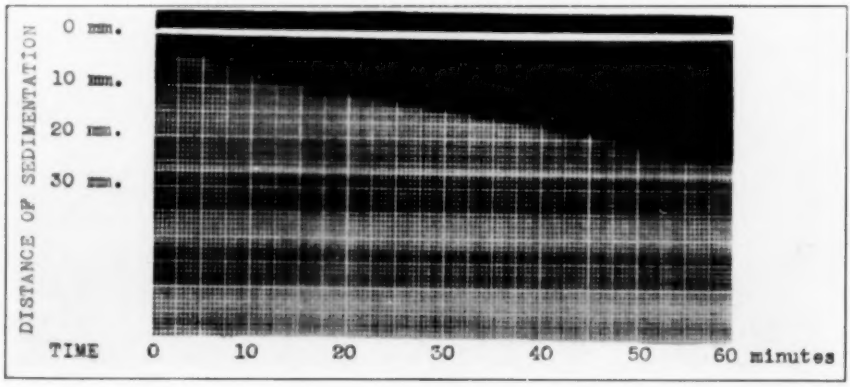


PLATE II.

PLATES I AND II.—Photographic records of the suspension stability or sedimentation rate of two specimens of blood.

of this exposure. This is important, since during the period of aggregation which occurs in the first phase of the sedimentation, there is little or no fall of the blood corpuscles.

A number is cut through the outer portion of the receptacle, just to the left of the receptacle in the manner of a window. This number is covered by a small elliptical aluminum disk. The disk is fastened to the receptacle by means of a pin eccentrically placed and may be turned about this pin. The disk is rotated to one side and the electric lights are turned on for a period of 30 seconds before the hematocrit is inserted in the receptacle. This procedure exposes the photographic paper to the number by which it may be identified.

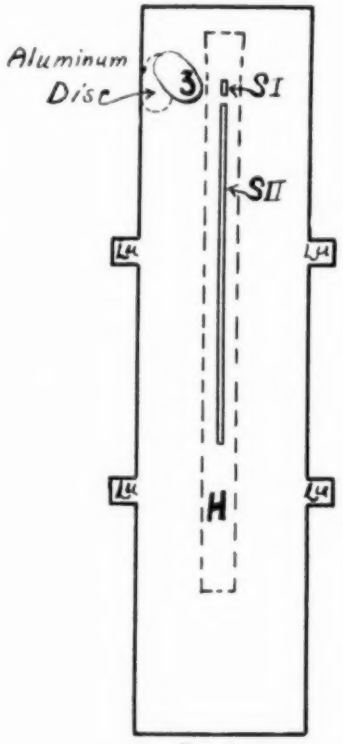
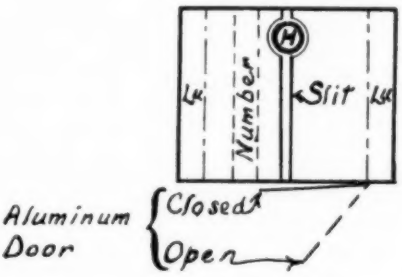


FIG. 4.



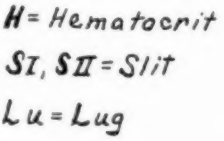


FIG. 5.

FIGS. 4 and 5.—Vertical and plan views of the receptacle with the hematocrits in place.

A rectangular aluminum door 150 by 22 mm. covers the slits when the instrument or any receptacle is not in use. While the instrument is in operation, the aluminum door covers the slits of the receptacle not in use, and they may be swung aside at any time that one desires to set up a sedimentation test in these receptacles.

The kymograph drum is similar to those used in physiologic work. The preferable diameter is from 18 to 25 cm. The height of the drum will depend on the number of determinations one desires to carry out at the same time. For the Wintrobe hematocrit filled to the 100-mm. mark, one

should allow 70 mm. height of the drum for each row of receptacles. This height seems adequate for in our work, using oxalate as an anticoagulant, the maximum fall of blood corpuscles which was observed in 1 hour was 60 mm.

The drum is driven by motion transmitted from a clock.* Ordinary alarm clocks* are very satisfactory for this purpose. The crystal, dial, and hands are removed from the clock. A small hole is made in the center of a No. 2 gum rubber stopper and the hour-hand pinion of the clock is forced into this hole. A piece of copper wire is placed around the stopper and tightened in the manner of a twisted ligature. A pulley is attached to the pinion of the kymograph drum and contact is made between this and the rubber stopper attached to the clock by means of a soft rubber or leather belt. The motion from the clock is thus transmitted to the drum. The pulleys are adjusted in ratio to permit a point on the surface of the drum to travel at the rate of 120 mm. per hour. Gears are preferable in place of the belt and pulley arrangement, but this increases the cost of the instrument.

A high-contrast, light-sensitive photographic printing paper† such as is used in commercial photography is fastened to the drum. Cross-section tracing cloth is fastened over the photograph paper and in close contact with and surrounding same. In our work a mesh of one square millimeter was used, since it is a standard ware. If the use of such a fine mesh is confusing, linen tracing cloth may be ruled with India ink in any desired ruling. The tracing cloth may be used over again and if care is taken may be used for several hundred determinations.

An interval-timer electric switch‡ makes contact with the light circuit and is also connected with a pulley in contact with the belt of the clock mechanism. The lever of the timer must be pushed to start the instrument and it is set to stop the clock mechanism and break the circuit of the electric lamps, 1 hour after the last sedimentation is set up.

Directions for Operation of Apparatus. Photographic paper surmounted by cross-section tracing cloth is fastened to the kymograph drum. The aluminum disks covering the numbers are rotated to one side and the electric lights are turned on for a period of 30 seconds; the Wintrobe[7] hematocrit is filled to the 100-mm. mark with blood to which an anticoagulant has been added; the hematocrit is inserted at once in the receptacle (*R*) in the housing; the battery of electric lights (*L*) is turned on; the aluminum cover (*Al*) is turned aside; and the clock mechanism is started. The lever of the interval-timer electric switch is set to stop the instrument at 1 hour (or other desirable time) after the last hematocrit is inserted.

The photographic paper is removed and developed any time after the last determination is completed. The hematocrits are removed, centrifuged, total volume of packed red cells determined and correction in sedimentation rate is made for the degree of anemia or polycythemia.

* Slow speed kymograph drums may be used but they are quite expensive.

† A simpler method may be employed when fewer determinations are made at the same time. Electrocardiographic paper is exposed in the cross-section mechanism of the electrocardiograph. The paper is then loaded on the kymograph drum and the paper is exposed to the beam transmitted by the plasma as described above. This will give a suitable cross hatching upon development. However, due to the narrowness of the paper, a separate strip (of paper) is required for each row of four hematocrits. This plan may be carried out more extensively by first exposing large sheets of photographic paper, eliminating the use of tracing cloth.

‡ The interval-timer electric switch may be purchased from the Arthur H. Thomas Company, Philadelphia.

Since devising this apparatus, I have discovered a paper by Litten[8] whose apparatus is similar to the one here described. However, his apparatus is relatively more expensive, less automatic in operation, and only one sedimentation determination may be carried out at a time.

Summary. A photographic suspension stability apparatus based on the difference in density to light between plasma and plasma plus blood corpuscles has been described. Light is projected through the plasma in blood-filled hematocrits upon light sensitive photographic paper which is in constant motion. The photographic paper is later developed and fixed, thus presenting a permanent, accurate and continuous record of the suspension stability of the blood. The apparatus has the advantages that it is self-recording; it requires no attention after it has been started; the number of determinations is only limited by the size of the instrument; and the records are free from the personal equation of an observer.

The author wishes to express his sincere appreciation for the kind assistance and coöperation of Dr. M. M. Wintrobe, who has assisted in the work with innumerable suggestions and supervised the preparation of the manuscript.

J. H. Emerson of Cambridge, Mass., is prepared to supply the instrument described in this paper.

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THE HEMATOPOIETIC RESPONSE OF THE RAT TO INJECTIONS OF PENTNUCLEOTIDE, AND ITS RELATION TO THE TREATMENT OF AGRANULOCYTOSIS.

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Following the work of Jackson,[1] who first demonstrated the existence of pentose nucleotides in normal blood, derivatives of nucleic acid in various forms have been used in the treatment of neutropenic states. The latest preparation, known commercially as pentnucleotide, is being employed widely in cases of agranulo-

TABLE 1.—RATS INJECTED WITH NUCLEOTIDE.

Rat No.	Date.	Peripheral blood.									Bone marrow.						
		W.B.C.	Poly. neutrophils, per cent.		Lymphocytes, total per cent.	Lymphocytes, per cent.			Monocytes, per cent.	Eosinophils, per cent.	Poly. neutrophils, per cent.	Eosinophils, per cent.	Lymphocytes, per cent.	Myeloblasts, per cent.	Myelocytes, per cent.	Erythroblasts, per cent.	Reticulocytes, per cent.
			Mature.	Band forms.		Y	M	O									
1	Before Jan. 12	6000	12	0	88	54	38	8	..	..							4.6
	After Jan. 19	5600	20	..	74	45	45	10	6	..	46.7	1.0	2.5	0.8	20.8	28.2	2.6
2	Before Jan. 12	6400	16	..	80	17	57	26	4	..		..					6.0
	After Jan. 19	3800	14	..	78	10	48	42	4	4	49.0	..	6.5	2.8	19.4	22.3	8.0
3	Before Jan. 11	3800	20	..	80	55	42	3	..	..							14.0
	After Jan. 19	4400	12	..	84	33	47	20	4	..	42.6	0.8	12.2	2.4	16.0	26.0	14.0
4	Before Jan. 12	2900	12	..	82	26	48	26	6	..							6.4
	After Jan. 19	6200	20	..	66	15	63	22	4	..	32.4	0.6	9.0	7.0	21.4	29.6	1.9
5	Before Jan. 11	4400	6	..	90	18	70	12	4	..							5.8
	After Jan. 19	7000	18	..	78	15	64	21	4	..	17.0	..	6.0	5.0	9.0	63.0	2.8
6	Before Jan. 6	6800	15	..	85	20	65	15	..	..							17.0
	After Jan. 14	5200	14	..	82	14	73	13	4	..	28.6	..	28.0	2.0	19.8	21.6	7.8
7	Before Dec. 19	4600	12	..	88	23	54	23	..	..							7.2
	After Dec. 30	6800	24	..	76	44	44	12	..	..	26.8	..	30.0	3.6	18.6	21.0	8.0
8	Before Dec. 19	3200	24	..	72	0	87	13	4	..							10.0
	After Dec. 30	6300	30	..	70	20	65	15	..	..	30.6	..	19.4	2.8	23.0	24.2	8.2
9	Before Dec. 19	3800	31	..	62	29	48	23	5	2							6.5
	After Jan. 10	6400	33	..	61	30	48	22	4	2	36.8	0.6	10.8	2.2	19.8	29.8	7.8
10	Before Dec. 19	3600	24	..	68	17	50	33	8	..							11.4
	After Jan. 3	4200	27	..	68	20	44	36	5	..	22.4	0.8	26.6	3.4	24.0	22.8	9.0
11	Before Dec. 19	4400	15	..	78	36	55	9	7	..							5.2
	After Jan. 10	8800	28	..	68	38	32	30	4	..	29.0	0.4	18.8	2.8	23.0	26.0	4.8
12	Before Dec. 19	5200	23	..	66	15	66	19	4	2							4.2
	After Jan. 6	4400	14	..	80	22	56	22	6	..	32.4	0.4	24.4	4.6	21.0	17.2	5.8
13	Before Jan. 12	5000	10	..	90	33	44	23	..	..							3.8
	After Jan. 19	7200	10	..	86	16	58	26	4	..	38.8	..	18.2	2.4	21.6	19.0	5.1
14	Before Feb. 1	5800	14	..	84	22	48	30	2	..							8.4
	After Feb. 10	6600	9	..	87	16	62	22	3	1	28.4	..	19.0	1.6	26.0	25.0	7.8
15	Before Feb. 1	5600	11	..	89	21	58	21	..	..							4.0
	After Feb. 10	6400	16	..	82	16	63	21	2	..	31.8	0.4	16.4	3.4	18.2	29.8	5.8
16	Before Feb. 1	8600	9	..	89	27	58	15	2	..							5.6
	After Feb. 10	4700	24	..	72	4	63	33	..	..	26.8	0.2	18.4	3.2	18.8	32.6	4.8
17	Before Feb. 1	6000	9	..	88	27	61	12	2	1							6.2
	After Feb. 10	6400	18	..	80	14	68	18	..	2	32.4	0.4	19.8	2.4	18.2	26.8	8.4

Average "Before" 5100 15+.

Average "After" 5900 20+.

TABLE 2.—CONTROL RATS INJECTED WITH SALINE.

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Rat No.	Date.	Peripheral blood.									Bone marrow.						
		W.B.C.	Poly. neutrophils, per cent.		Lymphocytes, total per cent.	Lymphocytes, per cent.			Monocytes, per cent.	Eosinophils, per cent.	Poly. neutrophils, per cent.	Eosinophils, per cent.	Lymphocytes, per cent.	Myeloblasts, per cent.	Myelocytes, per cent.	Erythroblasts, per cent.	Reticulocytes, per cent.
			Mature.	Band forms.		Y	M	O									
1 . .	Before Dec. 19	2800	10	..	87	68	28	4	..	3							14.2
	After Jan. 10	7200	16	..	84	14	61	25	..	..	52.0	0.8	12.8	1.4	18.8	14.2	5.4
2 . .	Before Dec. 19	4600	4	..	84	35	52	13	12	..							8.0
	After Jan. 10	6600	25	..	70	29	52	19	4	1	32.4	..	19.8	3.6	22.0	22.2	7.3
3 . .	Before Dec. 19	5200	14	..	82	27	59	14	4	..							6.2
	After Jan. 10	7800	20	..	74	35	43	22	4	2	19.8	0.6	21.8	4.6	28.0	25.2	5.0
4 . .	Before Jan. 11	5400	2	..	98	51	39	10	..	..							5.4
	After Jan. 19	7000	12	..	86	25	69	6	2	..	39.6	..	18.6	2.4	21.6	18.2	2.0
5 . .	Before Jan. 11	6200	10	..	90	47	42	11	..	..							5.0
	After Jan. 19	6000	2	..	96	22	56	22	2	..	24.8	0.8	14.4	3.6	20.8	35.6	5.4
6 . .	Before Jan. 11	8200	12	..	84	30	57	13	2	2							4.4
	After Jan. 19	6800	12	..	84	0	60	40	4	..	21.0	0.8	23.6	3.6	30.0	21.0	4.4
7 . .	Before Jan. 12	4800	26	..	68	38	50	12	6	..							4.2
	After Jan. 19	5000	28	..	70	37	47	16	..	2	42.6	0.8	18.2	1.8	16.4	20.2	3.4
8 . .	Before Jan. 11	7000	6	..	94	27	57	16	..	..							4.6
	After Jan. 19	7200	12	..	88	45	45	10	..	..	20.0	0.4	19.6	6.8	28.2	25.0	3.6
9 . .	Before Jan. 6	4000	30	..	70	62	34	4	..	..							8.9
	After Jan. 15	4300	26	..	72	28	48	24	2	..	25.8	..	36.8	2.8	17.0	17.6	7.6
10 . .	Before Jan. 11	6200	10	..	90	43	51	6	..	..							8.9
	After Jan. 19	5000	14	..	86	25	59	16	..	..	17.6	..	29.4	4.6	20.4	28.0	4.2
11 . .	Before Feb. 1	4800	9	..	87	22	64	14	3	1							5.0
	After Feb. 10	4600	18	..	78	16	68	16	2	2	28.4	0.8	16.8	3.0	18.2	32.8	5.5
12 . .	Before Feb. 1	4800	5	..	95	18	61	21	..	..							8.6
	After Feb. 10	5600	16	..	84	14	62	24	..	..	32.4	0.4	12.8	4.0	19.8	30.6	6.2
13 . .	Before Feb. 1	7400	16	..	82	29	51	20	1	1							5.8
	After Feb. 10	5400	14	..	85	26	42	32	..	1	32.4	0.8	18.4	2.6	21.4	24.4	6.4
14 . .	Before Feb. 1	4800	14	..	82	30	62	8	4	..							6.8
	After Feb. 10	6600	22	..	78	20	65	15	..	..	36.4	0.4	18.2	2.2	14.8	28.0	4.8
15 . .	Before Feb. 1	5200	22	..	68	27	48	25	9	1							5.2
	After Feb. 10	6600	16	..	79	30	52	18	4	1	27.2	0.3	20.0	4.5	15.3	32.7	5.6
16 . .	Before Feb. 1	3400	26	..	72	25	58	17	2	..							4.3
	After Feb. 10	5400	15	..	82	40	47	13	3	..	41.3	..	11.9	3.8	17.0	26.0	7.1
17 . .	Before Feb. 1	4800	32	..	56	17	53	30	12	..							8.0
	After Feb. 10	4800	25	..	71	32	43	25	1	3	18.0	0.6	29.2	4.0	20.0	28.2	8.7

Average "Before" 5300 14.6.

Average "After" 6000 17.1.

Average "Before" 5100 15+.

Average "After" 5900 20+.

cytosis. Jackson[2] and his coworkers have reported very good results from this method of therapy, while Rosenthal,[3] Fitzhugh and Comroe[4] consider these preparations to be of doubtful value.

A study of the bone marrow in cases of agranulocytosis has revealed that it can be either aplastic or hyperplastic. Fitzhugh and Krumbhaar[5] suggest a maturation arrest as the fundamental pathologic basis in those cases which show a hyperplastic marrow. The pentose nucleotides are supposed to have a positive chemotactic and maturative effect on myeloid foci and should therefore improve the delivery of granular leukocytes to the peripheral circulation.

Our own clinical experience with pentnucleotide has not been very conclusive, and it seems to us that those cases of agranulocytosis which improved after injections of this substance might have recovered as well without its use.

With these facts in mind, we decided to try the effects of pentnucleotide on the blood and bone marrow of an animal whose peripheral circulation is normally in a neutropenic state. Young rats were found to answer this requirement, as their blood normally shows a leukopenia with a low relative percentage of polymorphonuclear leukocytes. On one group of animals the effects of repeated injections of large doses of pentnucleotide alone were studied, while in another group the bone marrow was first depressed with benzol before the nucleotide was injected. Control groups of rats in which saline was injected instead of nucleotide were run at the same time. The peripheral blood and bone marrow were examined in each case for evidence of stimulating or maturative effects of the injections on the blood cells.

In the blood the Schilling count, lymphocytic index[6, 7] and reticulocyte percentage were employed as criteria of these changes, while the bone-marrow cells were studied in smears.[8, 9]

Technique.—The rats used were about 4 to 6 weeks old. For the experiment with nucleotide alone, single counts were done on all the animals before the injections were begun. One-half was then given daily injections of 1 cc. of pentnucleotide for 7 days, while the controls were given 1 cc. saline daily for the same length of time. Counts (single) were then repeated on the entire group and they were killed and bone-marrow smears made from the femur. For the experiment with benzol and nucleotide, another group of rats was selected and all were given daily injections of $\frac{1}{8}$ cc. of benzol in olive oil until the total leukocyte count in the blood was about 400. This required about 7 injections. Several of these rats were killed and the bone-marrow was found to be almost devoid of polymorphonuclear leukocytes. One-half of the remaining group was now given daily injections of 1 cc. of pentnucleotide for 7 days and the other half was given 1 cc. of saline for the same length of time. Counts were then done and bone-marrow smears made as above. In doing the differential count, Wiseman's[6] Wright-Giemsa stain was employed and the polymorphonuclear leukocytes were classified according to the Schilling index, while the lymphocytes were divided into *Y*, *M*, and *O* forms to determine their state of maturity. The reticulocytes were studied on fixed preparations vitally stained with cresyl blue and counterstained with Wright's stain, 1000 red cells being

examined in making the counts. The bone-marrow smears were made on slides and stained with Jenner-Giemsa stain, the Giemsa stain being left on the slide for ½ hour. A differential count of 1000 cells was done using a square diaphragm in the ocular, such as is used in enumerating reticulocytes.

TABLE 3.—RATS INJECTED WITH BENZOL FOLLOWED BY NUCLEOTIDE.

		Peripheral blood (final count).								Bone marrow.					
Rat No.	W.B.C.	Poly. neutrophils, mature per cent.	Lymphocytes, total per cent.	Lymph., per cent.			Monocytes, per cent.	Eosinophils, per cent.	Reticulocytes, per cent.	Poly. neutrophils, per cent.	Eosinophils, per cent.	Lymphocytes, per cent.	Myeloblasts, per cent.	Myelocytes, per cent.	Erythroblasts, per cent.
				Y	*M*	*O*									
1	2400	42	48	51	39	10	10	..	4.6	12.2	1.4	27.6	10.0	22.8	26.0
2	1700	28	66	25	49	26	6	..	6.8	24.0	1.0	31.8	9.2	23.8	10.2
3	1100	34	58	20	60	20	8	..	1.4	28.4	0.6	31.2	7.2	12.0	20.6
4	3200	60	32	54	44	2	8	..	6.2	32.2	0.2	21.0	3.8	12.4	29.4
5	3400	26	62	26	48	26	12	..	5.8	32.2	0.4	18.8	4.8	16.2	27.6
6	2800	44	40	55	39	6	14	2	7.4	26.0	0.8	24.8	4.8	14.2	29.4
7	1900	22	67	40	36	24	11	..	2.2	14.0	0.8	24.4	9.8	23.2	27.8
8	2000	31	63	32	49	19	6	..	4.6	34.6	0.8	19.4	6.2	18.0	21.0
9	1400	42	56	53	45	2	2	..	2.4	19.2	0.8	24.8	9.2	21.0	25.0
10	1600	46	44	12	50	38	8	2	8.2	36.2	0.2	14.0	4.8	16.2	38.6
11	5400	19	76	27	54	19	4	1	5.6	32.4	0.4	18.8	6.2	19.0	23.2
12	6700	32	66	19	63	18	2	..	7.2	26.8	0.2	21.4	3.2	19.8	28.6
Av.	2800	35.5													
RATS INJECTED WITH BENZOL FOLLOWED BY SALINE.															
1	800	22	68	40	35	25	10	..	1.8	0.8	0	55.4	10.2	3.2	30.4
2	3600	64	30	8	60	32	6	..	3.4	33.0	1.0	22.2	4.8	14.2	24.8
3	2600	60	36	24	52	24	4	..	4.2	34.2	0.4	24.2	4.2	18.8	18.2
4	2100	36	60	45	47	8	4	..	3.2	14.0	1.0	25.2	8.2	18.8	32.8
5	1800	28	64	32	52	16	8	..	3.4	28.2	0.4	21.4	5.2	19.8	25.0
6	4600	24	70	33	56	11	6	..	6.6	34.0	0.4	19.8	4.2	18.2	23.4
7	3000	46	36	42	48	10	8	..	6.4	26.8	0.6	22.4	8.2	16.8	25.2
8	2300	34	61	18	49	33	5	..	6.8	31.4	0.8	18.0	4.8	19.2	25.8
9	2900	31	59	21	52	27	8	..	6.2	25.2	0.2	20.0	5.8	15.1	33.7
10	1700	40	56	30	45	15	4	..	5.8	28.2	1.1	21.2	7.4	15.0	27.1
11	3100	35	55	27	40	13	10	..	7.1	32.7	0.7	15.8	9.4	19.0	22.4
12	1500	24	69	36	35	29	7	..	4.5	13.0	0.3	25.7	6.3	20.3	34.4
Av.	2500	37													

The experimental data follow:

A study of the experimental data is rather surprising, because it reveals that in the case of the rat, injections of pentnucleotide have very little effect in stimulating or improving the maturation of the blood cells. The total white count, Schilling and lymphocytic indices, reticulocyte percentage and bone marrow differential react about the same after saline injections as after nucleotide. Regeneration after benzol poisoning occurs just as quickly with saline injections as with nucleotide.

This experimental finding is somewhat of a disappointment, because the theory expressed by Doan,[10] attributing to nucleic acid and to the nucleotides chemotactic, maturative and initiatory stimuli for neutrophil myelocytes, seemed to explain the beneficial action of blood transfusions and irradiation on agranulocytosis as

well. Blood transfusions were supposed to be helpful in that they supplied additional nucleotides to a circulation deficient in this respect. Small doses of Roentgen ray might act in causing a primary destruction of some of the intact myeloid foci with a liberation of autogenous nucleotide, which then could initiate the maturation and delivery of leukocytes from the remaining myeloid foci. Isaacs[11] has shown that Roentgen rays have a maturing effect on all types of blood cells, the myeloid, lymphoid and erythroid. If the Roentgen ray acts through the nucleotide mechanism, it seems logical that injections of nucleotide would improve the maturation of red cells as well as polymorphonuclear neutrophils. This has not been the case in our work. The doses of nucleotide were very large in proportion to the weight of the rats and should have been sufficient to cause the changes expected. It can be argued that the hematopoietic system of the rat is different from that of man, but if the rat's bone marrow was depressed by benzol just as in the case of man, it ought to be stimulated by the same agents which are supposed to stimulate the human bone marrow. It is further recognized that other possible variants prevent the deductions from the experiment from being applied unqualifiedly to the treatment of human agranulocytosis. It is conceivable that an agent might be potent for neutropenia produced in one way and not for that produced in another; it might restore a lowered count to normal but not raise a normal count above normal, and so on.

However, these findings emphasize the vital importance of adequate controls, may help to throw light on some of the disappointing results obtained in the treatment of agranulocytosis with nucleotide and may also lend support to those who believe that many cases of agranulocytosis recover by themselves, and that a large percentage of the beneficial results attributed to the various forms of therapy for this condition may just be coincidental.

Conclusions. 1. The stimulating and maturative effect of injections of pentnucleotide on the hematopoietic system of the rat was studied, both with and without preliminary benzol depression.

2. Control injections of normal saline produced results not significantly different from those of the nucleotide.

3. The practically negative experimental results cast some doubt on the value of pentnucleotide in the treatment of agranulocytosis.

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AN ANALYSIS OF SO-CALLED APLASTIC ANEMIA.

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"Aplastic" anemia is usually regarded as a well-defined, readily recognizable clinical entity. The more important clinical and hematologic features are thought of as being a direct result of progressive depression and final cessation of bone marrow activity, and aplasia of this tissue is the accepted pathologic finding.

Our experience leads us to believe that the classical criteria of aplastic anemia exclude from that category many cases of the same fundamental nature as those included therein. In a series of 13 cases, representing the total experience of this clinic during the last 15 years, evidence of blood regeneration was a common finding. Nevertheless, our study of these cases and review of the literature indicate that they are not essentially different from many cases ordinarily classed as "aplastic anemia." Of these cases 2 followed exposure to benzol, 1 was apparently associated with prolonged exposure to Roentgen rays, while in the remaining 10 no contact with any known marrow poison was found and the clinical diagnosis of iodiopathic aplastic anemia was made.

The clinical features of all were similar, the outstanding feature being a progressive depletion in the number of circulating red cells, white cells and platelets. Evidence of regeneration appeared in all, with variation in size and shape of the red cells, increased reticulocyte counts, and occasional normoblasts as evidence of erythrogenic activity. In all a shift to the left of the white cells suggested leucogenic activity.

Study of the bone marrow revealed a wide variation in microscopic appearance. In 3 there was obvious hypoplasia of the bone marrow elements. In 2 the marrow appeared normal. In 2 moderate hyperplasia was seen and in the remaining 6 definite and marked hyperactivity was noted. The individual cases will be briefly presented, to be followed by an analysis and summary of the various findings.

Case Abstracts. Case 1 (No. 80886). An Irish man, aged 53, admitted to the wards with a 3 months' history of progressive weakness and pallor. On admission there was moderate emaciation, extreme pallor, no purpura, and an enlarged spleen palpable just below the costal margin.

R. B. C., 1,800,000; Hgb., 32 per cent; W. B. C., 1200; Pmn., 20 per cent; platelets, 77,000. There was marked variation in the size, shape and staining of the red cells and occasional normoblasts were seen. Notwithstanding the small number of neutrophils there was a definite shift to the left, with occasional myelocytes and rare myeloblasts. In spite of 8 transfusions and large amounts of liver extract and iron, the course was progressively downhill, and he died 6 months after the onset of symptoms, with a final clinical diagnosis of idiopathic aplastic anemia. At *autopsy* the femur marrow was found to be cellular with normal marrow elements appearing in normal numbers and in normal distribution. Examination of the other organs showed no anatomic basis for the hypocythemia.

Case 2 (No. 233329).—A Jewess, aged 37, was admitted with 2 months' history of progressive weakness and pallor. There had been no contact with any known industrial or chemical poisoning. On admission the patient presented extreme pallor but no evidence of loss of weight. Menorrhagia appeared and persisted and occasional petechiæ were noticed. The spleen could not be felt. R. B. C., 750,000; Hgb., 20 per cent; W. B. C., 2000; Pmn., 47 per cent; platelets, 22,000. There was moderate variation in size, shape and staining of the red cells with occasional normoblasts. The reticulocytes numbered 5.7 per cent. Occasional myelocytes were seen. In spite of 25 transfusions, large amounts of liver and liver extract, ventriculin, hydrochloric acid and iron, the course was progressive and the patient died 14 months after the onset of symptoms, with a final clinical diagnosis of idiopathic aplastic anemia. Marrow removed from the vertebra and femur at *autopsy* was very cellular, showing abundant blood formation with many clusters of nucleated red cells in various stages of development, many "stem cells," a normal or slightly increased number of myelocytes of all types and a slight reduction in megakaryocytes. Examination of the other organs showed no anatomic basis for the hypocythemia.

Case 3 (No. 276310).—An American physician, aged 70, who for many years had been engaged in experimental work with Roentgen rays and had had 1 finger removed following a carcinomatous change in a Roentgen ray burn, came into the hospital with a 5 months' history of increasing weakness, dyspnea, and pallor. There had been no loss of weight and no purpura. R. B. C., 2,000,000; Hgb., 50 per cent; W. B. C., 1400; Pmn., 32 per cent; platelets, 39,000. There was moderate variation in size and shape of the red cells and normoblasts were seen in all the smears. There was a distinct shift to the left in the white cells, with occasional myelocytes and rare myeloblasts. A reticulocyte count was not done. In spite of 4 transfusions and nucleic acid by mouth, the patient failed rapidly and died 6 months after the onset of symptoms. The final clinical diagnosis was aplastic anemia, secondary to Roentgen ray poisoning. At *autopsy*, marrow from the femur showed definite hyperplasia, with a moderate increase in the number of developing cells of the red and white cell series and marked increase in the number of megakaryocytes. There was, in addition, a muscular dystrophy of the Charcot-Marie-Hoffman-Tooth type. Examination of the other organs showed no anatomic basis for the hypocythemia.

Case 4 (No. 326119).—A Polish Jew, aged 48, entered the hospital with a 3 weeks' history of rapidly progressive weakness and pallor. There had been no loss of weight. The spleen was not enlarged. There were many petechiæ, but no ecchymoses. R. B. C., 1,500,000; Hgb., 35 per cent; W. B. C., 2500; Pmn., 12 per cent; platelets, 69,000. There was moderate variation in size and shape of the red cells and nucleated red cells appeared in numbers varying between 1 and 5 per hundred W. B. C. Reticulocytes, 1 per cent. There was a marked shift in the white cells and shortly before death 30 per cent myeloblasts were found. In spite of 2 transfusions and

several intramuscular injections of nucleotide, the patient failed rapidly and died 1 month after the onset of symptoms. Although it was felt that the clinical diagnosis was probably aplastic anemia, the possibility of acute leukemia was seriously considered. At *autopsy*, marrow removed from a rib and femur showed moderate hypoplasia, all the elements being present, but in reduced numbers. There were many plasma cells in both femoral and rib marrows and an increased amount of fat. There were no changes suggesting acute leukemia. Examination of the other organs showed nothing of note.

Case 5 (No. 298171).—A Greek stamp collector, aged 37, was admitted with a 4 months' history of progressive weakness and pallor. There had been no loss of weight and no bleeding. There was no enlargement of the spleen and lymph nodes. R. B. C., 1,200,000; Hgb., 20 per cent; W. B. C., 1400; Pmn., 49 per cent; platelets, 9000. There was moderate variation in size and shape of the red cells, the reticulocytes varied from 0.1 to 1.4 per cent and rare normoblasts were seen throughout the course. There was a persistent, though variable, increase in the number of young granulocytes. A terminal increase in myeloblasts up to 28 per cent of the white cells strongly suggested acute leukemia in the aleukemic phase. In spite of repeated transfusions, large amounts of liver and liver extract, nucleic acid and iron, there was a progressive, slow decrease in the number of cellular elements in the blood, and the patient died 13 months after the onset of symptoms. The clinical diagnosis was idiopathic aplastic anemia. At *autopsy*, the marrow removed from the femur, rib and vertebra was extremely cellular. There were many groups of developing erythrocytes, both early and late. Myelocytes were abundant in various stages of growth. Megakaryocytes were present in normal or slightly reduced numbers. There was no evidence of leukemia. Examination of the other organs showed no anatomic basis for the hypocythemia.

Case 6 (No. 303995).—A red-headed Irish boy, aged 25, who came in with a 6 months' history of progressive weakness and pallor, had had no loss of weight, but occasional nose bleeds and occasional purpuric spots. Examination showed many small purpuric spots. There was no enlargement of the spleen or lymph nodes. Tourniquet test was positive. R. B. C., 2,000,000; Hgb., 40 per cent; W. B. C., 1700; Pmn., 19 per cent; platelets, 14,000. There was moderate variation in size and shape of the red cells with occasional normoblasts at all times. Reticulocytes varied from 1.4 to 6.3 per cent. Young neutrophils and occasional myelocytes were present throughout. In spite of many transfusions, large amounts of liver, nucleotide, ventriculin and iron, the course was progressive and the patient died 14 months after the onset of symptoms. At *autopsy*, the marrow from the femur and rib was definitely hypoplastic, the normal cellular elements being largely replaced by a mass of plasma cells and lymphocytes. Except for an old, scarred duodenal ulcer, examination of the other organs showed no anatomic basis for the hypocythemia.

Case 7 (No. 328957).—An American man, aged 41, was admitted with a 2 months' history of increasing weakness and pallor. He had had several profuse nose bleeds and occasional ecchymoses. On admission the tourniquet test was found to be negative. There were many small purpuric spots and petechiæ. The spleen was just palpable. R. B. C., 2,900,000; Hgb., 45 per cent; W. B. C., 3100; Pmn., 12 per cent; platelets, 21,000. There was moderate variation in size and shape of the red cells. Nucleated red cells appeared in 1 to 5 per hundred W. B. C. Reticulocytes, 0.7 per cent. In spite of the low granulocyte count, there was a gradually increasing number of myelocytes and myeloblasts until shortly before death, when 35 per cent of the white cells were myeloblasts. In spite of 4 transfusions, intramuscular nucleotide, large amounts of parenteral liver extract

and iron, the course was progressive and the patient died 4 months after the onset of symptoms. Because of a large number of embryonic white cells the final clinical diagnosis was acute aleukemic myeloid leukemia. At *autopsy*, marrow from the femur was aplastic with much fat and only occasional small islands of developing cells. There were, however, many islands of extramedullary blood formation in the liver, spleen and lymph nodes. There was no evidence of leukemia. Examination of the other organs revealed no anatomic basis for the hypocythemia.

Case 8 (No. 339588).—An American man, aged 61, who was admitted with a 4 months' history of progressive weakness and pallor. On admission he was critically ill with a high fever and evidence of pneumonia in both lungs. No petechiæ or purpuric spots. There was a large sloughing ulcer of the palate. The spleen could not be felt. R. B. C., 1,400,000; Hgb., 30 per cent; W. B. C., 150; Pmn., 16 per cent; platelets markedly decreased. Reticulocytes were not counted. There was marked variation in size and shape of the red cells and much basophilic stippling. There were many nucleated red cells and occasional megaloblasts. Myelocytes were present in small numbers. He was given 2 transfusions, but died the 2d day. The final diagnosis was idiopathic aplastic anemia and terminal pneumonia. At *autopsy*, marrow removed from the femur, rib and vertebra was extremely hyperplastic, containing large numbers of young cells, both of the red and white series, in all stages of development, and a normal number of megakaryocytes. Examination of the other organs showed nothing of note except a bilateral confluent bronchopneumonia.

Case 9 (No. 352884).—An American man, aged 59, was admitted with an 8 months' history of progressive weakness, pallor and loss of 62 pounds in weight. For 2 years, ending 1.5 years before the onset of symptoms, he had been in daily contact with benzol fumes. There had been no purpura. The spleen was not enlarged. R. B. C., 1,400,000; Hgb., 30 per cent; W. B. C., 750; Pmn., 4 per cent; platelets, 36,000; reticulocytes, 0.1 to 1.4 per cent. There was moderate variation in size and shape of red cells and rare normoblasts were found in all the smears. Occasional myelocytes and rare myeloblasts were seen. In spite of transfusions, parenteral liver extract and a high vitamin diet, the patient failed rapidly and died 8.5 months after the onset of symptoms. It was of interest that although a carious tooth was extracted when the total white cell count was below 500 no ulceration appeared. The final diagnosis was "aplastic" anemia, possibly secondary to exposure to benzol. A sternal puncture was done 8 days before death, which showed an extremely active, cellular marrow with many young cells of all types in all stages of development. At *autopsy*, marrow removed from the femur, rib and vertebra was distinctly less cellular than the marrow of the sternum, but contained an apparently normal number of young red cells and white cells, as well as a definitely increased number of megakaryocytes. Examination of the other organs showed no anatomic basis for the hypocythemia.

Case 10 (No. 364427).—An American man, aged 53, who came in with a 2 years' history of progressive weakness and pallor. For several months immediately preceding the onset of symptoms he had been exposed to large amounts of benzol fumes while working in an unventilated photographic dark room. The present illness began with a nose bleed which was shortly followed by purpuric spots and progressive pallor. On admission the spleen was enlarged, reaching 2 cm. below the costal margin. There was no enlargement of the lymph nodes. R. B. C., 2,400,000; Hgb., 55 per cent; W. B. C., 1800; Pmn., 52 per cent; platelets, 18,000; reticulocytes, 18 per cent. Normoblasts 1 to 10 per hundred W. B. C. There was moderate variation in size and shape of the red cells with marked basophilic stippling. The white cells showed a shift to the left, with occasional myel-

ocytes and rare myeloblasts. In spite of transfusions, parenteral liver extract, large amounts of iron and nucleotide, he failed rapidly. He developed bilateral bronchopneumonia and died shortly after admission. The final diagnosis was "aplastic" anemia due to benzol poisoning, bronchopneumonia, terminal hemolytic streptococcus bacteremia. At *autopsy*, the marrow removed from the sternum, rib, femur and vertebra was the same in all instances and consisted of a mass of early myelocytes and erythroblasts. The myelocytic hyperplasia of the marrow was almost as extensive as that seen in chronic myeloid leukemia. There was no evidence of leukemia elsewhere in the body. The spleen weighed 370 grams and contained, as did the liver, scattered islands of blood formation. There was a terminal pneumonia and a very recent implantation of streptococci on the tricuspid valve. This case illustrates, apparently, the extreme myeloid activity that may occur as a late result of bone marrow injury.*

Case 11 (No. 350651).—A German Jew, aged 58, was admitted with a 2 months' history of progressive weakness and pallor. There had been no loss of weight. The spleen was enlarged to 2 cm. below the costal margin. R. B. C., 1,600,000; Hgb., 33 per cent; W. B. C., 800; Pmn., 16 per cent; platelets, 1800; reticulocytes, 5.2 per cent. Nucleated red cells 2 to 5 per hundred W. B. C. There was moderate variation in size and shape of the red cells. Myelocytes and myeloblasts appeared up to 10 per cent of the white cells. In spite of transfusions, parenteral liver, nucleotide, various vitamins and iron, the patient failed and died 5 months after the onset of symptoms. *Biopsy:* Permission for autopsy was not granted, but antemortem removal of a specimen of marrow from the sternum revealed almost complete aplasia of the marrow elements with replacement by connective tissue and fat.

Case 12 (No. 356328).—A young Norwegian, aged 27, who came into the hospital with a 12 months' history of progressive weakness and pallor. There was no enlargement of the spleen and lymph nodes, no loss of weight, and no petechiæ. R. B. C., 1,000,000; Hgb., 22 per cent; W. B. C., 1150; Pmn., 24 per cent; platelets, 20,000; reticulocytes, 3.3 per cent. There was moderate variation in size and shape of the red cells and occasional normoblasts were seen. There was again a shift to the left in the white cells and occasional myelocytes appeared in all preparations. *Biopsy:* Examination of the sternal bone marrow revealed a very cellular, extremely active marrow containing an increased number of all the normal elements, apparently in normal relative proportion. After several transfusions, the patient was discharged, at his request, to return to Norway. The final diagnosis was idiopathic "aplastic" anemia.

Case 13 (No. 268399).—An American-born Jew, aged 31, with a 7 years' history of slowly progressive weakness and pallor. The spleen was just palpable. There had been no purpura. R. B. C., 730,000; Hgb., 14 per cent; W. B. C., 1700; Pmn., 28 per cent; platelets, 9000; reticulocytes, 3 per cent. There was moderate variation in size and shape of the red cells with rare myelocytes and young polymorphonuclears. During the 7 years that he had been ill, he had received a total of 68 transfusions. While in this hospital he was given large amounts of pentnucleotide and intramuscular liver extract without response. *Biopsy:* Marrow removed from the sternum showed mild hypoplasia with a slight decrease in the number of young cells, although a considerable number of formative elements remained.

Analysis of Data. The more important findings revealed as follows:

1. *Sex.* Of the 13 cases 12 were males.

* This case will be published in detail by Dr. Dorothy H. Andersen.

2. *Age.* The youngest was 25 years of age, the oldest 70, and the average 46.

3. *Relevant Factors in the Past History.* In 2 of the 13, exposure to benzol fumes was definitely established. In Case 9 there had been an interval of 18 months between the last exposure and the first symptom. In Case 10 extensive exposure continued up to the clinical onset of the disease. In Case 3 excessive and prolonged exposure to Roentgen ray was thought to be of considerable etiologic importance. Nothing that could even remotely be considered as a relevant causal possibility was found in the other cases. A variety of nationalities and an assortment of occupations existed. There was no evidence of preliminary infection and no suggestion of familial occurrence.

4. *Symptoms.* In 10 of the 13 cases the disease began insidiously with weakness and pallor, in only 3 did purpuric manifestations signal the onset or appear during the course. The symptoms in all were the symptoms of progressive anemia.

5. *Physical Examination.* There was little or no evidence of loss of weight. The striking physical finding was the extreme pallor without the lemon-yellow tinge seen in the presence of increased red cell destruction. In 3 there were purpuric spots of various sizes, in 2 others occasional petechiæ were seen, in 8 there was no evidence of increased bleeding. In 2 the spleen was enlarged to 2 to 4 cm. below the costal margin, in 3 others it was just palpable at the end of inspiration, in 8 it could not be felt at any time.

6. *The Blood Picture.* The one outstanding feature of this group of cases was the progressive depletion of the number of formed elements in the peripheral blood.

(*a*) *The Red Blood Cells.* At the time of admission to the wards the number of red blood cells per c.mm. averaged 1,500,000. There was in the whole group surprisingly little variation from this number. Following transfusions transient rises in the red count occurred, but the degree, as well as the duration, of the response became less and less as time went on. The hemoglobin (corrected Sahli technique) averaged 20 per cent on admission, the color index remaining near 1 throughout.

(*b*) *The White Blood Cells.* There was a persistent leukopenia in all cases, the average admission white count being 1500 per c.mm., the highest 3100 and the lowest 150. In all there was a marked reduction in the percentage of neutrophils, the highest being 52 per cent, the lowest 4 per cent and the average 25 per cent.

(*c*) *Platelets.* With the exception of one platelet count of 77,000 per c.mm., all platelet counts in all cases were below 50,000.

(*d*) *Reticulocytes.* The percentage of reticulated red cells varied considerably, the lowest being 0.1 per cent and the highest 18 per cent. Variations occurred in the same individual with irregular changes from time to time. In the majority of cases, however, the reticulocytes were slightly to moderately increased.

(*e*) *The Blood Smears.* Wright stained coverslip preparations revealed changes quite different from the accepted aplastic anemia blood picture.

In all of the cases the red blood cells showed considerable to marked variations in size, in shape, in hemoglobin content and in staining reaction. There was no constant trend in the size of the cells, no definite tendency to macro- or microcytosis. The poikilocytosis was not as marked as in cases of pernicious anemia but was very definite. In all cases there was some polychromasia and in two the degree of basophilic stippling was extreme. In addition normoblasts were seen in all cases, varying from a relatively small number up to 8 to 10 per 100 W. B. C.

In spite of neutropenia, there was, in all cases, a definite shift to the left in the granulocytes. In all cases myelocytes were seen and in all but 3 myeloblasts were occasionally noted. In 3 cases the percentage of embryonic granulocytes reached sufficient proportions to warrant the consideration of acute leukemia as a possible final diagnosis.

(*f*) In 8 of the 13 cases there was no evidence of increased blood destruction and the urobilin excretion and serum bilirubin fell within normal limits. These determinations were not done in the remaining 5 cases.

7. *The Bone Marrow.* In sharp contrast to the uniform clinical and hematologic picture was the appearance of the bone marrow. In only 1 of the 13 cases was the marrow that was examined found to be aplastic. In 2 others there was moderate hypoplasia, in 3 the marrow appeared morphologically normal. In the remaining 7 the marrow was extremely cellular with marked increase in one or more of the developing cell types. In 3 of these 7 there was a general hyperplasia of all the elements, in 2 the hyperplasia was most apparent in erythroblastic activity, in 1 a marked increase in megakaryocytes was noted, in addition to an increase in red and white cell development, and in 1, a case of benzol poisoning, the marrow was filled with myelocytes in various stages of development. There was no postmortem evidence of leukemia in any case, nor was any anatomic basis for the condition found. Neither was there any reason for believing that any of these cases should have been considered as examples of pernicious anemia, thrombocytopenic purpura or agranulocytosis.

Discussion. There are several obvious, major discrepancies between aplastic anemia as it is usually described in the textbooks and "aplastic" anemia as we have seen it in this clinic. These discrepancies require explanation. Three possible explanations exist.

1. In the first place it is possible that, through some queer error in normal probability, there has not been a case of aplastic anemia in this hospital during the past 15 years. If the clinical diagnosis of aplastic anemia is rigidly limited to the usual specifications all of the above cases should have been given another name. If we

accept the absence of evidence of regeneration in the peripheral blood as an essential feature of typical aplastic anemia, if we require for diagnosis a fulminating disease with high fever and rapid course, then the clinicians of this hospital erred. If aplasia of the bone marrow is the major requirement at autopsy, we have seen only 1 case of aplastic anemia from the pathologist's point of view and our pathologists have erred in calling any of the other 12 cases "aplastic." If, on the other hand, progressive hypocythemia is the only requirement, all of the above cases meet that requirement and our diagnoses are sustained. In other words the clinical and anatomic diagnosis depends entirely upon one's definition of the syndrome, and a statement of the requirements and restrictions that must be met.

2. In the second place, it is possible that the requirements for diagnosis as set forth in various textbooks and reviews may not be entirely supported by the available clinical evidence. With this possibility in mind, examination of the literature revealed several points of interest.

The first case of "aplastic" anemia on record and the one most frequently referred to is that of Ehrlich.[1] The clinical and hematologic data are meager and questionable (the red count is reported as 213,000, a white count was not done, the platelets are not mentioned, the tibial marrow appeared yellow and fatty). Following this publication there appeared, from time to time, case reports of patients presenting similar pictures. By 1908 Cabot[2] was able to collect 24 cases and Hirshfeld,[3] in 1911, found the total to be 44. Musser[4] reviewed the situation up to 1914. In 1919, in a careful survey of the subject, Smith[5] collected and analyzed 64 cases of aplastic anemia. Although he appreciated the incompleteness of many of the recorded cases, he felt that the disease was uniform and readily recognizable, that it occurred chiefly in young adults (average age 29.5 years), that it progressed rapidly (average duration 3 months) and that it was characterized by a progressive decrease in the number of formed elements in the blood. There was an absolute lack of all young forms and the marrow was fatty in all cases. The conclusions arrived at by Smith express the opinions of the previous authors. For the most comprehensive recent reviews, the articles by Root[6] and Carey and Taylor[7] may be consulted. The latter authors find the 1931 total of reported cases reaching 150.

Perusal of these reviews would tend to convince one that idiopathic aplastic anemia is a uniformly acute, rapidly fatal disease of adolescents and young adults, that it is associated with a high fever, a rapid decrease in the cells of the blood, that there is never any suggestion of regeneration of these blood cells and that "at necropsy the marrow shows practically complete fatty degeneration."[8]

If, however, the individual case reports on which the reviews are

based are examined, the clinical, hematologic and pathologic findings do not always conform to the expressed requirements. Many of these reviews include cases so inadequately studied as to render them useless for analysis. Adequate blood counts may be lacking, often there is no description of the blood smears and, in a surprisingly large number, there was no microscopic examination of the bone marrow. In addition cases are included that, on closer examination, present definite variations from the accepted and stated standards, cases in which evidence of regeneration was present, cases in which the marrow was not fatty.

If analysis is restricted to those case reports that are complete and detailed, three variants of "aplastic" anemia become apparent. It is obvious that cases occur that conform, in all respects, to the accepted picture. If the cases of, for example, Muir,[9] Lavenson[10] and Smith[5] are examined, it is obvious that there is, without question, a disease of young people, acute and fulminating in its course, with a rapid decrease in the cellular elements of the blood, without evidence of regeneration, and with a complete aplasia of the marrow at necropsy. In addition, there is a second group comprising a few cases whose clinical features are similar to the preceding group, but in which the marrow, instead of being fatty, was found to have a normal or even increased cellular content. Such cases have been reported by Naegeli,[11] Senator,[12] Wolff[13] and Root[6] and several appear in the Italian literature[14,15,16] under the name of "pseudo-aplastic" anemia, a term suggested by Luzzatto[15] to indicate the discrepancy between the blood and bone marrow picture. The third variation comprises cases of progressive hypocythemia in which evidence of regeneration appeared in the peripheral blood, such as in the detailed reports of Blumer,[17] Sabrazes, Micheleau and Mandillon,[18] Di Guglielmo (1928), Merklen and Wolf,[23] and the cases observed by us. In some of these cases (all but one of ours) the marrow was found to be cellular, so that the question is raised as to whether this condition of the marrow could not have been diagnosed correctly from examination of the blood. However, in the 1 case in our series in which the marrow of the sternum was aplastic, immature cells appeared in the circulation in numbers as great as in the other 12 cases, apparently coming from extramedullary foci or from hyperplastic foci in the marrow of bones not examined. Also, in Di Guglielmo's cases (1928) it was found that immature red and white cells appeared with fatty marrow. This author lays particular emphasis on the occurrence of immature cells, and states that the essential character of the disease, from the hematologic standpoint, "is not the absolute absence of erythroblasts during the whole course, but the irreducible and progressive diminution of the number of the morphological elements of the blood"—a feature which we also consider essential, and to which we have referred as "progressive hypocythemia."

It is extremely difficult to obtain a clear idea of the clinical, hematologic and pathologic pictures of the disease in the majority of these case reports. In a great many of the older records confusion with pernicious anemia exists. Reticulocyte counts, leukocyte "shifts," platelet counts, were not a part of the routine technique and adequate marrow preparations are lacking. But from even such a brief presentation of the acceptable records it would seem that the diagnosis of aplastic anemia had been stretched at times so as to include fairly obvious variations from the previously accepted standards.

3. A third possible explanation of the discrepancies existing within our group, and between our cases and the accepted descriptions, exists. It would seem possible to have a progressive decrease in the number of circulating blood elements as a result of a variety of causal agents acting on the marrow; that although the peripheral blood pictures might be in many ways similar, the terminal microscopic appearance of the marrow might vary with the nature of the disturbing agent, with the type of injury sustained, with the degree of regeneration permitted, with the piece of marrow examined or even the time of examination. Some such explanation would seem to be the most compatible with the evidence at hand.

There is no question but that progressive hypocythemia may be secondary to various marrow toxic agents, the most widely studied of these being benzol. It is now known that the morphologic appearance of bone marrow previously injured with this chemical is far from uniform. In most animal experiments and in most human cases, chronic benzol poisoning results in aplasia of the marrow. But in some experimental animals[19] and in some human cases (such as Dr. Cabot's case report,[20] the case of Martland quoted by Hamilton[24] and Case 10 in our group) the marrow was found to be hyperplastic and it is important that in these, as well as the typical "aplastic" instances of benzol poisoning, the blood picture was that of progressive hypocythemia. What we seem to be dealing with in all is a severe disturbance in bone marrow function that may not invariably be correlated with bone marrow morphology. The peripheral results of the injury may be the same, but the visible effects on the marrow at the time of removal may be quite different.

This discrepancy between the functional activity of the marrow and the morphology of a minute fragment is seen in various other conditions. As examples: it is not uncommon to find a persistent leukopenia in cases of leukemia; the marrows of patients dying of agranulocytosis may appear normal or even hyperplastic as far as the granulocytic elements are concerned (Fitzhugh and Krumbhaar[21]); in pernicious anemia there is extreme hyperplasia of primitive red cells, and in many of the recorded examples of "gelatinous

degeneration" of the marrow the blood counts have been within normal limits.

Another difficulty appears when it is realized that the appearance of a fragment of marrow may be no indication of the state of this organ elsewhere in the body. That marked variation in cellularity may occur within a radius of a few millimeters is generally appreciated and has been thoroughly discussed by others.[22,23]

It would seem, therefore, that examination of the peripheral blood may be no index as to the morphologic appearance of the fragments of marrow examined and that the morphologic appearance of the marrow may be no index as to its functional activity.

Summary and Conclusion. 1. Thirteen cases of "aplastic" anemia have been studied. In all, the disease was characterized clinically by a progressive decrease in the number of erythrocytes, leukocytes and platelets—a progressive hypocythemia. In all, evidences of attempted regeneration were noted in the peripheral blood.

2. The marrow revealed a wide variation in microscopic appearance. In only 1 of the 13 was the marrow aplastic. In 2 it appeared hypoplastic, in 2 it was morphologically normal. In the remaining 8 there was moderate to marked hyperplasia of one or more of the formative elements.

3. It is felt that many of the restrictions and limitations placed on the clinical and pathologic diagnosis of "aplastic" anemia should be removed and that progressive hypocythemia alone should be sufficient reason for making the diagnosis, provided leukemia can be excluded.

4. The lack of correlation between the blood picture and bone marrow morphology has been discussed. It is felt that examination of the peripheral blood may be, at times, no index as to the condition of the blood-forming apparatus. Specifically, progressive hypocythemia as observed in these cases is not, in itself, sufficient evidence on which to postulate the presence of aplastic bone marrow.

5. This strongly suggests that it is quite possible to have serious interference with the normal processes of development, maturation and delivery of blood cells without evident alteration in the cellular content of the marrow.*

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* While accepting the probable correctness of the authors' thesis, it would seem as if the situation would be clarified by using for the present, at least different labels for the 3 varieties; thus, "aplastic anemia" might be reserved as many now do, for the type without evidence of regeneration in blood or bone marrow; "pseudo-aplastic anemia" for the variety with cellular bone marrow; and "progressive hypocythemia" for the kind here described, *i. e.*, with evidences of attempted regeneration in both blood and bone marrow.—EDITOR.

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THE BLOOD CYTOLOGY IN UNTREATED AND TREATED SYPHILIS.

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Improved methods for the study and differentiation of living cells based on physiologic activity has provided means for investigating blood and tissue reactions from a functional as well as a morphologic point of view. These methods have been applied to the study of syphilitic reactions in man[1] and animals.[2] The present report is concerned with the blood cytology, as determined by the supravital technique, of patients with untreated and with treated syphilis. A subsequent paper will discuss the blood cytology in the active and latent stages of the experimental disease.

Material and Methods. Observations were made on the blood cytology of 213 syphilitic patients.* Of these, 87 had received no treatment, and 126 had been variously treated before the blood examinations were made. The untreated group was composed of 48 patients with active primary infection, 23 patients who had active secondary lesions, and 16 who presented signs and symptoms of tertiary disease. The treated group consisted of 43 patients on whom treatment was started in the primary stage, 30 who had received their first treatment in the secondary stage, and 53 who began their treatment in the tertiary phase. The clinical diagnosis

* Through the kindness of Dr. Howard Fox, these patients were made available for study in the Syphilis Clinic of the University and Bellevue Hospital Medical College, New York University.

of syphilis was confirmed in all cases by dark-field or serologic examination. This report is essentially limited to the study of white males. Of the 213 patients, 29 were colored and 7 were females.

The blood examinations were conducted from November, 1930 to November, 1932; with the exception of March, 1931, and July, August and September of 1931 and 1932, counts were made every month during this interval. Since the patients were ambulatory and repeated counts could not readily be obtained, only one complete blood examination was made on each individual. Each examination included a total white and red cell count made with standardized automatic pipettes, a platelet count by the Ringer-heparin method of Casey,[3] a hemoglobin determination by the Newcomer method, and a differential white cell count, using the supravital neutral red technique, 100 cells being counted on each of two smears. The blood samples were taken in the afternoon, usually between 2.00 and 3.00 P.M., and examined later[4] the same afternoon. From 2 to 7 blood examinations were made on those afternoons devoted to this study. One observer made all the red cell, white cell, platelet and hemoglobin determinations, and all the differential smears were examined by the same two observers.

Most of the treated patients received alternating doses of neoarsphenamin and mercury, but many had been treated either entirely or at some time with various drugs, including bismuth, arsphenamin, sulpharsphenamin, silver arsphenamin and tryparsamid. The amount of treatment ranged from less than one course to several courses separated by rest periods. Classification on the basis of the drugs used, the dose and frequency of administration has not been attempted.

In the analysis of the results, the usual statistical methods were employed for determining the mean, the standard error of the mean, and the standard error of the difference of two means. A difference was considered significant when the probability of its occurrence by chance was less than one in 100 ($t = 2.5$, $P = 0.01$). The χ^2 method is that described by Fischer.[5]

It is usual in a study of the blood picture in any disease to indicate whether the findings are higher, lower, or the equivalent of normal values. In the present study there were two objections to this procedure. The normal limits of variation in the number of white blood cells in man is usually given as ranging between 5000 and 10,000, with an average of 7500. In our experience of weekly counts on a small group of normal young men over a period of 2 years,[6] the mean total white cell count was nearer 6500 than 7500. In addition to this discrepancy between accepted values and our own for the total white cell count, a second difficulty was the fact that, so far as is known, there has not yet appeared an adequate statistical survey of the differential cell formula of normal individuals as determined by the neutral red supravital technique, the method employed in this study. Because of these two facts, we have hesi-

tated to ascribe normality to any of the values obtained in this investigation.

We have, however, made an effort to determine the differences, if any existed, between the supravital and fixed smear methods in our hands. Duplicate counts were made on the first 86 patients of this series with the two techniques. The cover-slip method was employed in the preparation of the fixed smears, and 100 cells were counted on each of two smears after staining by Wright's method. A comparison of the mean values for the counts on these 86 individuals revealed that significant differences were present. Counts made with the supravital technique gave significantly higher values for neutrophils, basophils, and monocytes, and a significantly lower value for lymphocytes, than did duplicate counts on fixed smears. The eosinophils were slightly higher with the neutral red method, but this difference was not significant. (Neutrophils: Difference, 2.4 ± 0.97 per cent; t, 2.5; P, 0.01. Basophils: Difference, 0.3 ± 0.10 per cent; t, 3.0; P, 0.01. Monocytes: Difference, 1.7 ± 0.53 per cent; t, 3.2; P, 0.01. Lymphocytes: Difference, 4.7 ± 0.89 per cent; t, 5.3; P, 0.01. Eosinophils: Difference, 0.3 ± 0.29 per cent; t, 1.1; P, 0.2.) With the exception of the findings for monocytes, the direction of these differences was similar to that observed by Sabin.[7]

Since comparisons with normal values could not be made, the procedure adopted was to group the patients in a systematic manner, and compare the blood cell values of one group with those of another. In this way errors which might be due to variations in technique, in observers, and countries are mimimized.

Results. The essential findings are summarized in Tables 1 to 7. The values given in Tables 1 and 2 are represented graphically in Figure 1.

The Blood Cytology in Untreated Syphilis. The mean blood cell values of the untreated patients whose blood was examined in the primary, secondary or tertiary stages are shown in Table 1. No significant differences were found between any of the blood elements of the primary and secondary cases. The comparative infrequency of untreated tertiary syphilis is evidenced by the small number of individuals in this group. There were a sufficient number of observations, however, to show that the mean monocyte count was significantly lower than that for both the primary and secondary cases. (Primary: Difference, 297.8 ± 97.3; t, 3.06; P, 0.01. Secondary: Difference, 425.3 ± 115.7; t, 3.67; P, 0.01.) Of interest also is the low mean value for the red cell count in the tertiary group. This was significantly lower than the red cell count in the primary syphilitics, and probably significantly lower than the mean red cell count of the patients with secondary disease. (Primary: Difference, 437,000 ± 14,500; t, 3.01; P, 0.1. Secondary: Difference, 358,000 ± 17,300; t, 2.06; P, 0.05.) It will be noted that although

the differences were not statistically significant, the values for the total white cell count, platelet count and neutrophils were lower in tertiary syphilis, while the lymphocytes were higher than in either of the early stages. These differences no doubt would have been of greater significance had the number of patients

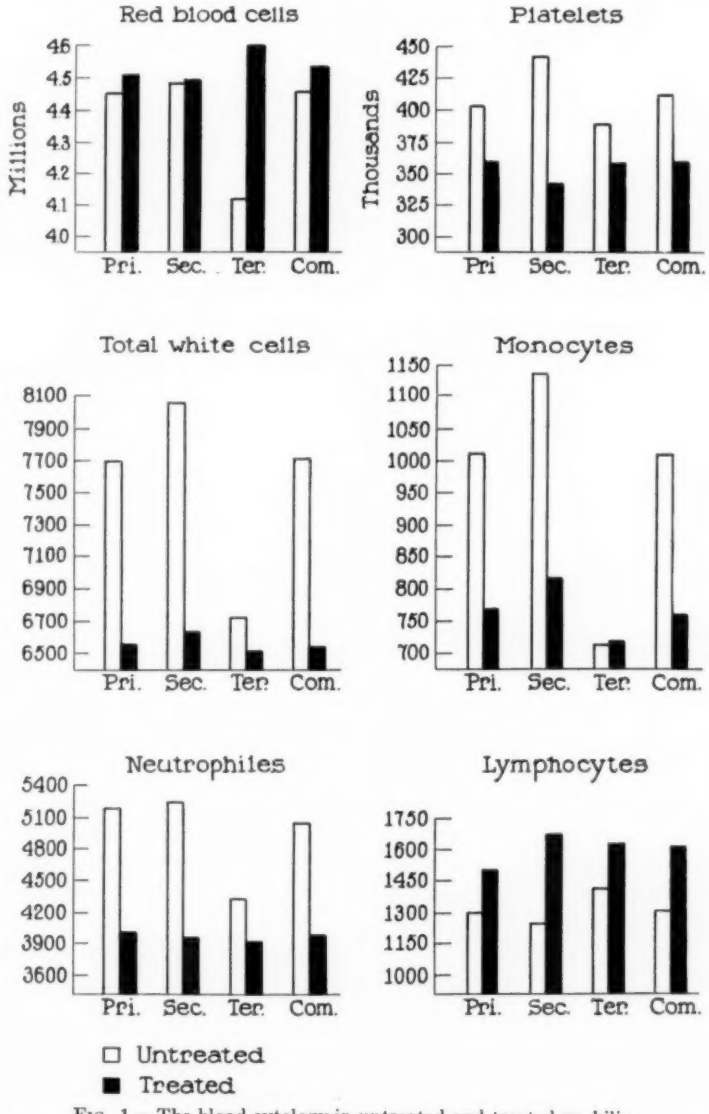

FIG. 1.—The blood cytology in untreated and treated syphilis. Pri., Sec., and Ter. refer to the Primary, Secondary and Tertiary stage. Com. indicates the combined values for all three stages.

in the tertiary group been larger. A comparison of the findings in late syphilis (tertiary stage) with the combined values for early syphilis (primary and secondary stages), gave two highly significant differences. In the late group of cases both the red cell count and the monocyte count were significantly lower than the corresponding values for the early syphilis group. (Red cells—combined primary and secondary group: n, 71; tertiary group: n^1, 16. $Mean_n$, 4,530,600 ± 6,580. $Mean_n$, 4,119,000 ± 12,240. Difference, 411,600 ± 13,900; t, 2.96; P, 0.01. Monocytes — $Mean_n$, 1,051 ± 49. $Mean_n$, 712 ± 77. Difference, 339 ± 91; t, 3.71; P, 0.01.) On the same basis none of the other blood elements showed any statistically significant differences.

TABLE 1.—THE MEAN AND STANDARD ERROR OF THE MEAN OF THE BLOOD CONSTITUENTS IN UNTREATED SYPHILIS.

Stage.	No.	Value.	R. B. C.	H.	P.	W. B. C.	N.	B.	E.	L.	M.
Primary	48	Mean	+000 4456	% 69.0	+000 403	7696	5187	37	155	1306	1010
		Standard error of mean	±77.1	±1.3	±5.2	±278.8	±233.6	±8.3	±21.0	±40.7	±59.9
Secondary	23	Mean	4477	63.8	441	8052	5247	63	323	1277	1137
		Standard error of mean	±123.5	±1.8	±25.7	±529.1	±377.5	±13.4	±82.8	±113.6	±86.7
Tertiary	16	Mean	4119	65.5	389	6716	4355	62	184	1409	712
		Standard error of mean	±122.5	±1.7	±22.3	±442.9	±365.4	±11.8	±36.7	±115.9	±76.8
Total	87	Mean	4455	67.0	411	7610	5050	48	205	1316	989
		Standard error of mean	±60.7	±1.0	±9.4	±228.7	±179.9	±6.5	±26.7	±51.0	±45.0

R. B. C., red blood cell count; W. B. C., white blood cell count; P., platelet count; H., hemoglobin; N., neutrophils; B., basophils; E., eosinophils; L., lymphocytes; M., monocytes.

The Blood Cytology in Treated Syphilis (Table 2). Three subdivisions were employed in the analysis of these results, depending on whether treatment was begun in the primary, secondary or tertiary stage of the disease. No significant differences were observed in the blood formulæ of the three groups.

Comparison of the Results for Treated and Untreated Syphilis. The differences in the untreated and treated groups (Tables 1 and 2) were submitted to a further analysis. The mean values for the combined untreated group of 87 patients were compared with those of the combined treated group of 126 patients. In the treated group, the total white cell count was lower, the platelet count was lower, the hemoglobin in per cent was higher, the absolute number of lymphocytes was higher, and the absolute number of neutrophils and of monocytes was lower, than the corresponding values for the

untreated group. (Total white cells—Difference, 1,051 ± 275; t, 3.8; P, 0.01. Platelets—Difference, 53,000 ± 11,000; t, 4.7; P, 0.01. Hemoglobin—Difference, 5.3 ± 1.10 per cent; t, 3.6; P, 0.01. Neutrophils—Difference, 1,084 ± 210; t, 5.2; P, 0.01. Lymphocytes—Difference, 290 ± 69; t, 4.2; P, 0.01. Monocytes—Difference, 228 ± 51; t, 4.5; P, 0.01.) No difference was observed between the two groups with respect to the red cell count or the absolute numbers of eosinophils and basophils.

TABLE 2.—THE MEAN AND STANDARD ERROR OF THE MEAN OF THE BLOOD CONSTITUENTS IN TREATED SYPHILIS.

Stage.	No.	Value.	R. B. C.	H.	P.	W. B. C.	N.	B.	E.	L.	M.
			+000	%	+000						
Primary	43	Mean	4511	72.5	358	6563	4039	59	192	1502	771
		Standard error of mean	±90.0	±1.1	±11.5	±238.2	±179.9	±9.8	±29.2	±74.9	±39.2
		Mean	4487	72.9	341	6632	3941	46	147	1677	821
Secondary	30	Standard error of mean	±104.9	±1.9	±18.3	±318.6	±228.3	±9.8	±23.0	±124.4	±52.7
		Mean	4599	71.6	358	6511	3921	50	172	1650	718
Tertiary	53	Standard error of mean	±104.9	±1.5	±9.9	±254.9	±171.2	±13.5	±17.3	±59.5	±37.0
		Mean	4542	72.3	358	6559	3966	52	174	1606	761
Total	126	Standard error of mean	±53.8	±0.8	±6.2	±153.2	±107.6	±6.2	±13.3	±46.5	±24.1

R. B. C., red blood cell count; W. B. C., white blood cell count; P., platelet count; H., hemoglobin; N., neutrophils; B., basophils; E., eosinophils; L., lymphocytes; M., monocytes. The designations, *primary*, *secondary* and *tertiary*, refer to the stage in which treatment was begun.

In relative percent the same differences were noted between the white cell formulæ of the treated and untreated groups as for the absolute numbers of the white cell components (Table 3). It will be seen that the neutrophils and monocytes of the treated group were lower, and the lymphocytes higher, than the corresponding cells in the untreated group.

TABLE 3.—MEAN BLOOD CELL VALUES IN PER CENT IN 87 CASES OF UNTREATED AND 126 CASES OF TREATED SYPHILIS.

	Neutrophils.		Basophils.		Eosinophils.		Lymphocytes.		Monocytes.	
	Untr.	Tr.	Untr.	Tr.	Untr.	Tr.	Untr.	Tr.	Untr.	Tr.
	%	%	%	%	%	%	%	%	%	%
Mean . . .	65.6	59.8	0.6	0.7	2.7	2.6	17.9	24.9	13.1	11.7
Standard error of mean	±0.84	±0.77	±0.02	±0.02	±0.25	±0.26	±0.65	±0.64	±0.45	±0.32
Difference between means	5.8 ± 1.13		0.1 ± 0.11		0.1 ± 0.36		7.0 ± 0.91		1.4 ± 0.55	
t	5.2		0.9		0.3		7.7		2.6	
P	0.01		0.3		0.8		0.01		0.01	

Untr. = Untreated. Tr. = Treated.

Discussion. Thus the mean cell values of the total treated group of 126 patients differed from those of the untreated group of 87 patients in the following respects: Lower total white cell count, platelet, neutrophil and monocyte counts, and higher values for lymphocytes and hemoglobin. There are certain factors in the material itself which might have influenced these differences. These will be discussed in order.

Number of Observations. One factor which might account for the observed differences is the disproportion between the numbers of patients in the treated and untreated groups. The untreated series had only 16 patients in the tertiary group, while the treated series contained 53 patients who received their first specific treatment in the tertiary stage (Tables 1 and 2). Could this bias account for the differences between the blood cells of treated and untreated cases? If tertiary cases are omitted from both groups, and a comparison is made between the 71 untreated patients with early syphilis (primary and secondary stages), and the 73 patients treated in the early period, the two groups are more nearly comparable as far as numbers are concerned than if the total treated and untreated groups are considered. But the same differences are apparent as were observed between the total treated and untreated groups (Table 4). The total white count, the platelet count, the neutrophil and monocyte counts in the 73 treated patients were lower, and the lymphocyte count and the hemoglobin in per cent were higher, than the same values for the 71 untreated patients. There was no difference between the red cell values or the numbers of basophils and eosinophils in the two groups. It is evident, therefore, that the disproportion in the number of observations in the two groups did not introduce sufficient bias to account for the differences.

Age. The observed differences were not associated with any differences in age. The mean age of the 87 untreated patients was 32.7 ± 1.37 years, while the mean age of the 126 treated patients was 36.2 ± 0.94 years. The difference of 3.5 ± 1.66 is not of statistical significance since it is only 2.1 times the standard error of the difference.

Sex, Color and Time of Counting. Of the 213 patients examined, 96.7 per cent were males, and 86.4 per cent were white. A bias which might be introduced by sex and color is therefore not effective in the present series. Since all counts were made in the afternoon, time of the day is not a factor which can account for the differences.

Duration of Infection. It has been shown that the values for the total white cell count, platelets, neutrophils and monocytes of the untreated late syphilis group were lower, and the lymphocytes higher, than the corresponding values for untreated early syphilis. These differences were similar in direction and affected the same cells as the differences noted between the untreated and treated early syphilis groups. Thus the values for untreated late syphilis

TABLE 4.—MEAN BLOOD CELL VALUES IN 73 CASES OF UNTREATED SYPHILIS AND 71 CASES OF TREATED SYPHILIS. COMBINED VALUES FOR PRIMARY AND SECONDARY STAGE.

	Platelets.		Hemoglobin.		White blood cells.		Neutrophils.		Lymphocytes.		Monocytes.	
	Untr.	Tr.	Untr.	Tr.	Untr.	Tr.	Untr.	Tr.	Untr.	Tr.	Untr.	Tr.
Mean	+000 416	+000 351	% 67 3	% 72 7	7812	6577	5206	3999	1296	1574	1051	792
Standard error of mean	±9 8	±10 1	±1 18	±0 69	±255 9	±190 6	±200 0	±138 9	±94 4	±67 8	±49 4	±31 6
Difference between means	65 ± 14 0		5 4 ± 1 37		1235 ± 319		1207 ± 243 4		278 ± 116 2		259 ± 58.7	
t	4 6		3 9		3 9		4 9		2 4		4 4	
P	0 01		0 01		0 01		0 01		0 015		0 01	

Untr. = Untreated. Tr. = Treated.

and those for treated early syphilis differed in the same manner from the values for the untreated patients with early syphilis. It is evident therefore that the duration of the infection is a factor which affects changes in the blood cytology independent of treatment, since many years may elapse between the primary and secondary stages of infection and the occurrence of tertiary disease. On the same basis it is possible that the changes observed in the treated group as compared with the untreated group might have been influenced by spontaneous variations occurring during the period required for treatment, and that these differences might have developed regardless of the institution of treatment. With this possibility in mind, a further analysis of the results was made.

Of the patients whose first treatment was begun in the primary stage, all cases were selected in which from 1 to 6 months had elapsed between the time of the first evidence of infection and the time when the blood cytology was studied. This group of 19 treated primary cases was compared with the 47 untreated cases of primary infection. The same differences were observed between the mean blood cell values of these two groups as were found between the combined treated and untreated groups.

It is evident, therefore, that the observed differences between the treated and untreated groups were associated directly with the institution of anti-syphilitic measures. It is of interest to recall the somewhat similar observations of Hazen.[8] He found that, under treatment, either with mercury or salvarsan or a combination of the two drugs, cases of syphilis show a fall in the total white count and percentage of neutrophils, and a rise in the percentage of lymphocytes. Moreover, the administration of mercury to a group of non-syphilitics caused a slight fall in the total white count and in the relative neutrophil count, and a rise in the relative lymphocyte count. A fall in the number of platelets after treatment

has been observed by Mu,[9] while Cummer[10] and Eason[11] and others have commented on the anemia of tertiary syphilis.

The Monocyte and Lymphocyte in Syphilis. The monocyte-lymphocyte ratio, which has been suggested by Cunningham, Sabin and their coworkers as a prognostic aid in tuberculosis, is of especial interest in the present observations. The mean M/L index for the total untreated group of this study was 0.80, while the total treated group gave a significantly lower M/L index of 0.52. This difference was due to a significantly higher lymphocyte and a significantly lower monocyte level in the treated group. The occurrence of an M/L index of less than 0.55 in the treated group, or of more than 0.55 in the untreated group, was significantly more frequent than would be expected from random association ($\chi^2 = 29.51$; n = 1, P = 0.01). Not only were differences noted between the M/L indices of the untreated and treated groups, but within the treated group also such differences were observed. Among the treated patients there were 20 individuals whose Wassermann was repeatedly negative after intensive treatment. The M/L index of this group was 0.34. The average M/L index of a group of 25 patients whose Wassermann reaction was positive on more than one occasion after prolonged treatment was 0.60. Thus there appeared to be a relationship between the numbers of lymphocytes and monocytes in the blood stream and activity of the disease on the one hand, and the efficacy of treatment as evidenced by the Wassermann reaction on the other. This relationship was investigated more precisely.

The group of 20 persistently treated patients with negative Wassermann reactions, and the group of 25 persistently treated

TABLE 5.—INTENSIVELY TREATED SYPHILIS CASES CLASSIFIED AS TO BLOOD SEROLOGY AND M/L RATIO. OBSERVED AND EXPECTED VALUES.

	Observed.			Expected.		
	Less than 0.45.	0.45 or more.	Total.	Less than 0.45.	0.45 or more.	Total.
Wassermann positive	4	21	25	10	15	25
Wassermann negative	14	6	20	8	12	20
Total	18	27	45	18	27	45

patients with positive Wassermann reactions were utilized for the analysis. These groups were classified in two ways: as Wassermann positive or negative, and as having an M/L index of less than 0.45, or 0.45 and above (Table 5). The observed deviations from expectation were clearly significant ($\chi^2 = 13.50$; n = 1, P = 0.01). In other words there was a high positive correlation between Wassermann negativity and an M/L index lower than 0.45, and between Wassermann positivity and an M/L index higher than 0.45.

In a similar manner the lymphocytes and monocytes of the two groups were studied. Again the two groups of 20 and 25 treated

patients were classified in two ways: as Wassermann positive or negative, and as having a total lymphocyte count of less than 1350 or more than 1350 per cc. (Table 6). The observed findings were significantly independent of expectation ($\chi^2 = 8.10$; n= 1, P = 0.01). Put in another form, lymphocyte values higher than 1350 were more frequently associated with negative serology, and lymphocyte values under 1350 were more often associated with positive serology than could be expected from chance association.

The persistently treated group was again divided in two ways: as Wassermann positive or negative, and as having monocyte values of less than 700 or more than 700 per cc. The observed and expected values are presented in Table 7. The association of negative serology with monocytes less than 700, and of positive serology with monocytes more than 700 per cc. was significantly more frequent than would be expected from random association ($\chi^2 = 7.98$; n = 1, P = 0.01).

TABLE 6.—INTENSIVELY TREATED SYPHILIS CASES CLASSIFIED AS TO BLOOD SEROLOGY AND LYMPHOCYTES PER CC. OBSERVED AND EXPECTED VALUES.

	Observed.			Expected.		
	Less than 1350.	More than 1350.	Total.	Less than 1350.	More than 1350.	Total.
Wassermann positive	14	11	25	9.4	15.6	25
Wassermann negative	3	17	20	7.6	12.4	20
Total	17	28	45	17.0	28.0	45

TABLE 7.—INTENSIVELY TREATED SYPHILIS CASES CLASSIFIED AS TO BLOOD SEROLOGY AND MONOCYTES PER CC. OBSERVED AND EXPECTED VALUES.

	Observed.			Expected.		
	Less than 700.	More than 700.	Total.	Less than 700.	More than 700.	Total.
Wassermann positive	7	18	25	11.7	13.3	25
Wassermann negative	14	6	20	9.3	10.7	20
Total	21	24	45	21.0	24.0	45

Comparison of the Blood Cytology in Human and Experimental Syphilis. A study has been made of the blood cytology in the active and healed phases of experimental syphilis. It was found that certain differences existed between the mean blood cell values of rabbits with active syphilitic lesions and the values for normal control rabbits. In the syphilitic group the total white blood cells, the number of platelets, and the neutrophils and monocytes were significantly higher, while the lymphocytes were significantly lower than the corresponding values for normal animals. In the spontaneously healed or latent phase of the disease, when the rabbits presented no clinically demonstrable evidence of infection, the blood

cell values were not different from normal findings with two exceptions: the red blood cell count and the hemoglobin in per cent were lower.

These findings are of interest since they parallel so closely the observations on the human disease reported in this paper. In the human disease as has been stated, treatment causes a fall in the white blood cell count, platelet, neutrophil and monocyte counts, and a rise in the value for lymphocytes, from the findings in untreated patients. In the experimental disease, spontaneous regression without treatment is accompanied similarly by a fall in the white blood cell count, platelet count, neutrophil and monocyte counts, and a rise in the lymphocyte count.

Another parallelism, between the red cells and hemoglobin of the human and experimental disease, is also striking. With the exception of the red cells, all the blood elements of the untreated tertiary group showed the same changes from the findings in the untreated early syphilis group as were noted as a result of treatment. The marked depression of the red cells would seem to indicate that the prolonged infection affects them more severely than the other blood constituents. Similarly in the experimental disease, several months after inoculation when clinical signs of infection had disappeared spontaneously without treatment, the red cells and hemoglobin were significantly lower than normal values, although all the other cell elements had returned to normal levels. The only difference observed between the treated and untreated tertiary groups of humans were in the red cells and hemoglobin, both of which were significantly higher in the treated patients. (Red blood cell count —Difference, 480,000 ± 16,100; t, 3.0; P, 0.01. Hemoglobin —Difference, 6.1 ± 2.26 per cent; t, 2.7; P, 0.01.) Thus it would appear that specific treatment of the tertiary disease in the human causes a rise of the red cell count and hemoglobin value to higher levels, and it is quite probable that similar treatment of the experimental disease would do likewise.

Conclusions. It has been shown that the treatment of syphilis causes a fall in the total white cell and platelet counts, and the absolute and relative numbers of neutrophils and monocytes, and a rise in the absolute and relative numbers of lymphocytes from values observed in untreated syphilis. That these changes can occur without treatment is evidenced by the fact that changes similar in direction were observed in untreated tertiary syphilis as compared with untreated primary and secondary syphilis. Moreover the same differences were present between the values for treated as compared with untreated early syphilis. One may reasonably conclude that the institution of treatment facilitates the blood changes which occur without treatment if the disease progresses to the tertiary stage. Treatment however accomplishes one additional change in the blood picture, in that it is associated with a rise in the

red cell and hemoglobin levels from the low values found in untreated tertiary syphilis.

It has been found that an M/L index higher than 0.55 occurs more frequently in untreated syphilis, and an M/L index lower than 0.55 more frequently in treated cases than would be expected from random association. Moreover, a definite relationship has been found in persistently treated patients between the Wassermann reaction and the values for lymphocytes, monocytes, and the resulting M/L index. The use of the M/L index as a prognostic aid in evaluating the efficacy of treatment is suggested by these findings.

The parallelism in the blood cell changes that exist between the human and the experimental disease in the rabbit, is further evidence of the similarity between the pathologic processes in the two hosts, and lends additional weight to conclusions drawn from experimental syphilis as applied to the human disease.

Summary. From a study of the blood cytology of 126 treated and 87 untreated syphilis patients it was found that:

1. Treatment causes a fall in the total white cell count, the platelet count, and the relative and absolute numbers of neutrophils and monocytes, and a rise in the relative and absolute numbers of lymphocytes, and per cent hemoglobin, from values observed in the untreated cases.

2. No significant differences were noted between the mean blood cell values of the primary and secondary untreated patients.

3. A marked anemia was the outstanding feature of the blood cytology in the untreated tertiary disease. This anemia was absent in patients whose treatment was begun in the tertiary stage.

4. No differences in the blood cytology of treated patients were noted when treatment had been begun in the primary, secondary or tertiary stages of the disease.

5. A monocyte-lymphocyte ratio higher than 0.55 was more frequent among untreated patients, and a monocyte-lymphocyte ratio less than 0.55 was more frequent among treated patients, than would be expected from random association.

6. In a group of persistently treated patients, repeatedly negative serology was more frequently associated with a monocyte-lymphocyte ratio less than 0.45, with lymphocytes higher than 1350 per cc., and with monocytes less than 700 per cc.; and persistently positive serology was more frequently associated with a monocyte-lymphocyte ratio higher than 0.45, with lymphocytes lower than 1350 per cc., and with monocytes higher than 700 per cc. than would be expected from random association.

7. The changes observed in the cytology of the treated patients as compared with the untreated patients were similar in direction and affected the same cells as the changes observed in the spontaneously regressed experimental disease as compared with the

period of lesion activity. This similarity lends additional weight to deductions drawn from the experimental disease as applied to human syphilis.

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INVOLVEMENT OF THE EIGHTH NERVE IN SYPHILIS, WITH SPECIAL REFERENCE TO THE RESULTS OF TREATMENT.

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Alexander[1] reviewed, in 1929, the extensive literature concerning the diagnosis of syphilis of the 8th cranial nerve. The otologic findings most commonly recorded are: (1) A lowered upper tone limit; (2) loss of acuity for high tones, sometimes accompanied by a loss for middle or for all tones; (3) shortened bone conduction associated with "normal hearing," as first noted by Beck;[2] and (4) impaired vestibular responses. The hearing defects, with the exception of the 3d point, are the classical signs of all forms of nerve deafness. Wodak, Wanner and Rhese (quoted by Alexander) have disputed this point, since they found such shortened bone conduction as frequently in non-syphilitics as in patients with syphilis. If they are correct, then it would follow that a diagnosis of syphilis of the eighth nerve is usually based only upon the finding of a nerve type of deafness in a patient with syphilis.

Bearing this point always in mind, the authors have statistically analyzed audiometric and other records of the hearing of a group of individuals with syphilis. Attention has been focussed upon the question of the effect of antisyphilitic treatment upon hearing.

Material and Method. The material which forms the basis of this study is composed of 286 individuals with a well established diagnosis of syphilis. Some of these were examined as a part of the routine work of the Otological Research Laboratory, the others were referred from the Syphilis Division of the Medical Clinic of The Johns Hopkins Hospital following complaints on the part of the patients of some hearing defect or symptoms of vestibular disturbance.

The material, therefore, is not a random sampling, so that it is not possible to consider our data as representative of the incidence of inner ear disease in syphilis in general, or of the relative frequency in its various types. Bunch's audiometric data[3] show that the loss of acuity for high tones found in those with syphilis is on the average the same as in a general population, considering age and sex. Ciocco[4] reported that the incidence and degree of high tone loss in patients with all types of syphilis and in those with syphilis of the central nervous system is in no way different from that in non-syphilitics.

The hearing of each patient was examined with a Western Electric Company 1–A audiometer, supplemented in most cases by Weber, Schwabach and Rinne tests with a c^2 (512 d. v.) tuning fork. A Struycken monochord was used for the upper limit determination. All cases have been excluded in which there was a serious middle ear lesion or in which it was clear that the hearing defect antedated the acquisition of syphilis. The vestibular examination was limited usually to a cold caloric stimulation.

In Table 1 is given the race and sex distribution of the individuals studied, grouped according to the type of syphilis, as diagnosed in the Syphilis Division of the Medical Clinic.

TABLE 1.—DISTRIBUTION OF MATERIAL BY TYPE OF SYPHILIS, RACE AND SEX.

Type of syphilis.	White.			Colored.			Grand total.
	Males.	Females.	Total.	Males.	Females.	Total.	
Early	4	2	6	2	..	2	8
Late (excepting neurosyphilis) . . .	32	15	47	54	52	106	153
Neurosyphilis . . .	61	21	82	19	3	22	104
Congenital	7	10	17	1	3	4	21
Total	104	48	152	76	58	134	286

Classification of the Audiograms. The audiograms are assigned, according to the degree of hearing loss, into the groups described by Ciocco.[4] Typical examples of good hearing (I) and of the three degrees of high tone loss (II, III, IV) are shown in Fig. 1. On the basis of Ciocco's data on the distribution of these hearing groups,

by age and sex, in a general population our material is divided in to 3 yet larger groups. These are: (1) "Normal" hearing, including all with good hearing (Group I) and all of those with high tone loss of a degree within the expected limits for their age and sex; (2) "excessive high tone loss," in which are included those with a loss for high tones greater than would be expected for their age and sex; and (3) "subnormal" hearing, which includes those showing also a loss for low and middle tones. The individuals in this group have an impairment of hearing for speech varying from slight difficulty to total deafness. When the hearing loss is different for the two ears, the poorer one has been used in allocating the case to a group. Table 2 shows the distribution on this basis.

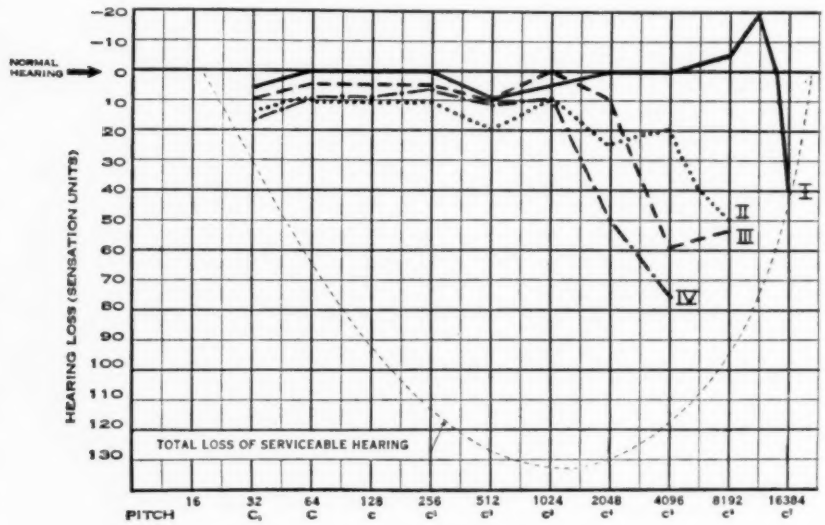

FIG. 1.—Representative audiograms of groups indicated. (From Ciocco, Laryngoscope, 1932.)

TABLE 2.—HEARING GROUP DISTRIBUTION ACCORDING TO AGE.

Age.	"Normal" hearing.	"Excessive high tone loss."	"Subnormal" hearing.	Total.
−20	7	1	4	12
20 to 29	29	12	10	51
30 to 39	37	24	16	77
40 to 49	48	25	8	81
50+	29	10	26	65
Total	150	72	64	286

A high percentage of the individuals with "subnormal" hearing are above the age of 50 years. Analysis of the case histories involved has not provided an explanation for this. It is highly improbable that this represents an effect of age on hearing entirely independent of syphilis.

Reliable histories as to time and nature of onset of symptoms were obtained from 44 of the 64 patients in the "subnormal" hearing group; the onset was sudden in 20 and gradual in 24; it occurred before the beginning of treatment in 27 and after in 17. In these patients the hearing loss was unilateral in 16 and bilateral in 28.

Bone Conduction. We have regarded bone conduction time as shortened only in those cases in which, after repeated trials, it was consistently much less than the particular examiner's "normal." On this basis there are, of the 203 satisfactorily tested for this point, 58 with shortened bone conduction. These are distributed as follows: In the "normal" hearing group, 5 out of 92 tested; in the "excessive high tone loss" group, 7 among 53; and in the "subnormal" group, 46 out of the 46 giving reliable responses. A definitely disproportionate shortening of bone conduction is present in only a relatively small number of our cases. Of the 5 patients with "normal" hearing and shortened bone conduction, 3 are over 60 years of age and 2 over 40 years. The significance of this, in view of our method of classifying, is only that of a shortened bone conduction in a high tone loss.

The Vestibular Reaction. No attempt has been made to evaluate diminished reactions of a slight degree, these being included with the entirely normal ones and being termed "normal." Markedly reduced reactions, grossly sluggish responses and no reaction have been grouped together as "impaired." The vestibular test was done in 119 cases. It was found "normal" in 88 and "impaired" in 31. Since 21 of these latter are among the 40 "subnormal" hearing cases which had vestibular tests, it is evident that in syphilis the incidence of impaired vestibular function is greater when there is a marked functional disturbance of the cochlear branch of the 8th nerve. About one-third of the cases with a vestibular disturbance are not accompanied by either shortened bone conduction or "subnormal" hearing.

Involvement of the 8th Nerve and Type of Syphilis. Alexander[1] states that the 8th nerve is involved in 20 per cent of those with latent syphilis and in 69 per cent of those with tabes and paresis, the latter figure being based on Krassnig's work. The distribution of the several forms of syphilis in our material among the 3 hearing groups is shown in Table 3.

TABLE 3.—HEARING GROUPS AND TYPE OF SYPHILIS.

Type of syphilis.	Hearing. "Normal."	"Excessive high tone loss."	"Subnormal."	Total.
Early	3	5	..	8
Late (excepting neurosyphilis)	102	30	21	153
Neurosyphilis	37	34	33	104
Congenital	8	3	10	21
Total	150	72	64	286

From it the incidence of nerve deafness in late syphilis (exclusive of neurosyphilis) would appear to be even greater than given by Alexander, and in neurosyphilis, including tabes and paresis, about the same as Krassnig gave. But since, as has been stated already, our material can in no sense be regarded as unselected, these values should not be considered as either confirmatory or contradictory.

Analyses of our cases from the standpoints of bone conduction and of vestibular reactions, as related to the several forms of syphilis, give results so similar to those for the audiometric data that these tabulations are omitted.

Reliable results were obtained in the same individuals for the bone conduction time and the vestibular reactions in 102 cases. In 18 of these are present all 3 of the most definite signs of involvement of the 8th nerve, *viz.*, loss of acuity for all tones by air conduction ("subnormal" hearing group), shortened bone conduction and impairment of vestibular reactions. The diagnoses for these 18 cases are: neurosyphilis, 12; congenital syphilis, 5; latent syphilis, 1.

Spinal Fluid Studies. Many observers have considered disturbance of function of the 8th nerve as evidence of central nervous system involvement in patients who had syphilis or in whom that diagnosis was suspected. Our material does not support this interpretation. The cerebrospinal fluid was examined in 106 of our patients with either "excessive high tone loss" or "subnormal" hearing. Thirty of these had late syphilis, exclusive of neurosyphilis, and the fluid was normal in all. In 64 with neurosyphilis the fluid was normal in 16 and abnormal in 48. Normal fluids were found in 11 of the 12 with congenital syphilis. Smith's[5] data are of interest in this connection; in a group of 33 congenital syphilitics with 8th nerve impairment, but without physical signs of neurosyphilis, the spinal fluid was abnormal in only 2. Obviously a diagnosis of neurosyphilis based only on impaired function of the 8th nerve in a patient with syphilis is not justified.

Involvement of Other Cranial Nerves. The function of other cranial nerves was impaired in 33 of our patients. The optic nerve was involved in 18; these patients are about equally distributed among our 3 hearing groups. In contrast to this, of 13 patients with facial nerve involvement, 8 are in the "subnormal," 3 in the "excessive high tone loss" and only 2 in the "normal" hearing group. The vestibular reactions were examined in 9 patients with facial paralysis and impairment was noted in 6, while this was true for only 2 of the 8 who were tested, who had optic nerve involvement.

The Effect of Antisyphilitic Treatment. Otologists and syphilologists are particularly interested in knowing what effect antisyphilitic treatment may have upon the hearing. Statistical reports by Beck[2] and Lund[6] and experimental studies by Ferretti[7] and others concerning the effect of arsphenamin and its various compounds point to the conclusion that the reported deleterious effects of these drugs have been exaggerated. Those patients with transitory

impairment of hearing following an injection probably suffer from a form of the Jarisch-Herxheimer reaction. Nerve deafness coming on 1 to 2 months following the inadequate treatment of early syphilis is considered to be not a toxic neuritis but a neurorecurrence. As to the beneficial effects of treatment, Alexander states that in 120 patients with congenital and acquired syphilis with impaired hearing, treated with neoarsphenamin and mercury, 8 per cent regained normal hearing, 42 per cent improved, 48 per cent remained unchanged and in 2 per cent the hearing became worse. Benario (quoted by Alexander) reported that in his cases of neurorecurrence the hearing was restored in 83 per cent while under treatment and improved in another 8 per cent; he regards the age of the patient and the method of treatment as important factors. Moore[8] noted improvement in all but 7 of 31 patients with neurorecurrence. Krassnig observed no improvement of hearing in deaf or partially deaf tabetics and paretics.

We have utilized two methods of approach in attempting to ascertain the effect of treatment upon hearing: (1) All of our cases have been grouped according to the amount of treatment received prior to the first audiometric examination and according to the hearing acuity at that time. (2) Those patients having 2 or more audiometric examinations have been analyzed separately from the standpoint of changes in hearing and the treatment received in the interval.

TABLE 4.—HEARING GROUPS AND AMOUNT OF TREATMENT.

	Hearing.			
Treatment.	"Normal."	"Excessive high tone loss."	"Subnormal."	Total.
Inadequate	118	55	55	228
Adequate	32	17	9	58
Total	150	72	64	286

The data obtained by the first method are presented in Table 4. The continuous plan of treatment outlined by Moore and Keidel[9] has been used. This consists of alternating series of an arsenical compound, usually arsphenamin, and a heavy metal, as a rule bismuth. The tabulation reveals that the majority of the patients had received little or no treatment before the date of otologic study. This is common to the 3 hearing groups. Only a small number are known to have had any treatment at all within 2 years following infection. Very few had received adequate* treatment before the hearing examination; these are proportionately distributed among the three groups. Many observers believe that lesions of the 8th nerve have been due to treatment with arsenical compounds. Our material shows that the majority of those with "subnormal" hearing have had little or no previous treatment. In particular, we have

* In this paper the treatment has been termed "adequate" on the basis of Moore and Keidel's definition.

no evidence in this series that in patients with already existing hearing difficulties the institution of treatment has been followed by further sudden abrupt deafness (Herxheimer reaction). Contrary to the widespread impression that inadequate treatment is more liable to enhance injury to the 8th nerve by syphilis, attention is called to the large number of such individuals in the "normal" hearing group.

On the whole, the above data justify the conclusion that in this group of patients no relationship is apparent between treatment and the development of hearing defects. Similar analyses from the standpoints of bone conduction and of vestibular reactions warrant the same conclusion.

Those patients having 2 or more otologic examinations are 61 in number. The intervals between the first and last tests vary from 2 months to 5 years, with an average interval of 2 years. There was no change in hearing in 52 of these, a diminution in 5, a slight improvement in 2 and marked improvement in 2.

The distribution as to hearing groups of the 52 whose hearing remained stationary is as follows: "normal" hearing, 23; "excessive high tone loss," 14; "subnormal" hearing, 15. Among these are 24 patients with late syphilis (excepting neurosyphilis), 24 with neurosyphilis, 3 with congenital syphilis and 1 with early syphilis. The amount of treatment was on the average the same for those in each of the 3 hearing groups.

Of the 5 patients whose hearing acuity decreased between the examinations, the loss in 3 is of the type that is characteristic of advancing age, being confined to the high tones; 2 of these had latent syphilis and 1 paresis. One of those with latent syphilis had received inadequate treatment; the other 2 had received regular treatment for about a year. The hearing acuity of 2 patients decreased for all tones; 1 had latent syphilis and 1 had involvement of the central nervous system. Both received adequate treatment. In both cases the vestibular reactions had also become impaired in the interval. The audiograms of the individual with the most striking change in hearing are given in Fig. 2. The patient is a colored man, aged 42, who gave no history of infection. The right facial nerve was paralyzed in 1925, and at that time he complained also of some impairment of hearing on the same side. The diagnosis made was central nervous system syphilis, unclassified. His hearing was first tested on March 3, 1930, after he had received adequate treatment, consisting as usual of alternating series of arsphenamin and bismuth. At that time bone conduction was not shortened and the vestibular reactions were "normal." Treatment was given regularly from that time until March 20, 1933. The audiograms of the ear that changed (Fig. 2) show the amount of loss for air conduction; the bone conduction had also become shortened and the vestibular reactions sluggish.

The slight improvement in hearing found in 2 cases was confined to the high tones; 1 had latent syphilis and received little treatment in the 6 months between the 2 otologic examinations, the other had tabes and received treatment continuously for over a year.

The audiograms of the 2 cases with improvement of a more marked degree are shown in Figs. 3 and 4. The greatest improvement observed was in a white woman, aged 29, who, while hospitalized

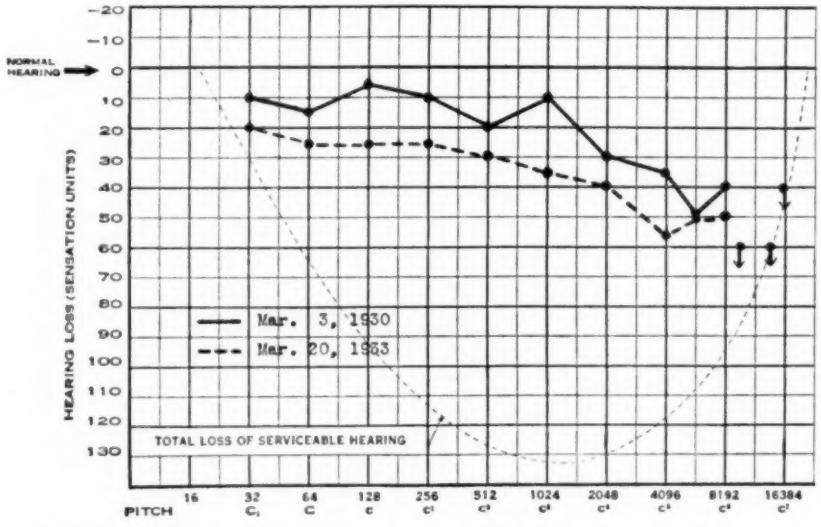

FIG. 2.—Decrease in hearing observed in a patient with neurosyphilis, unclassified.

for a fractured humerus, complained of a sudden disturbance in hearing. The audiogram of this date (December, 19, 1928, Fig. 3) shows a severe loss for air conduction; bone conduction time was also shortened. A vestibular examination was not made. She gave a questionable history of infection 2 months previously, for which she had received elsewhere 1 or 2 injections, probably arsphenamin. The blood Wassermann was positive and the spinal fluid negative. The recorded diagnosis was neurorecurrence. She was given weekly injections of arsphenamin (0.3 gm. each) for 6 weeks and then failed to return. The audiogram of March 9, 1933, 50 months after the first one, shows the marked improvement for air conduction; bone conduction was not shortened; the vestibular reactions at this time were normal.

Marked improvement, involving mostly the high tone region, was observed in a colored man, aged 26, who applied for treatment on September 9, 1931, with a genital chancre. During the next 5 months he received 4 injections of arsphenamin, the last one in February, 1932. Four months later he returned with a neuro-

recurrence involving the 5th, 7th and 8th cranial nerves. Both blood and spinal fluid Wassermann reactions were positive. At this time, June 7, 1932, the first otologic examination was made. The audiogram (Fig. 4) revealed a moderate degree of high tone loss; bone conduction time was not shortened; the vestibular

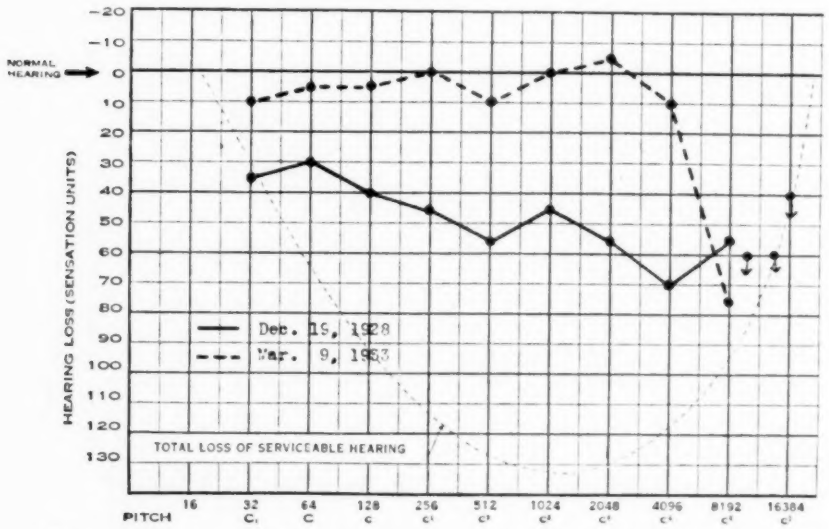

FIG. 3.—Improvement in hearing observed in a patient with early meningeal neurosyphilis (neurorecurrence).

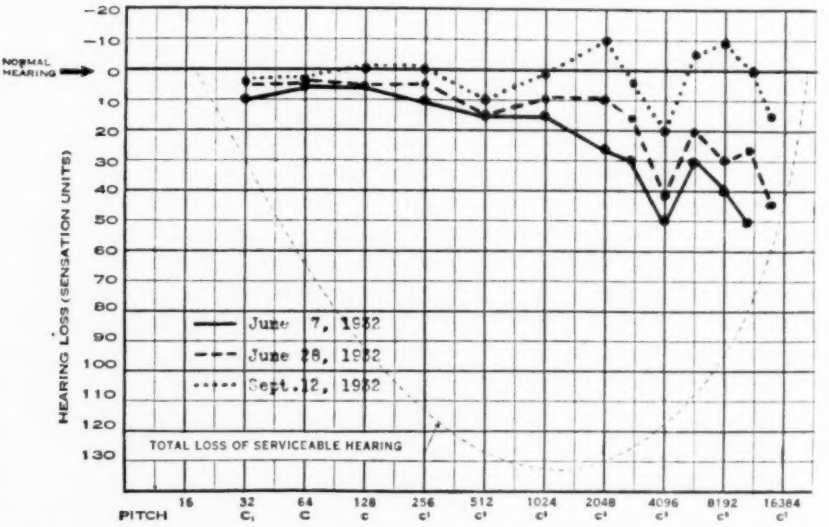

FIG. 4.—Improvement in hearing observed in a patient with early meningeal neurosyphilis (neurorecurrence).

responses were sluggish. Regular treatment was resumed. The audiogram made 3 weeks later (June 28) shows some improvement, and that of 3 months later (September 12) a return to good hearing. Vestibular reactions were now normal. During this 3 months he had received 14 injections of arsphenamin and 11 of bismuth.

Since the hearing remained stationary in 85 per cent of the 61 patients who had 2 or more otologic examinations, the number of those whose hearing changed is too small to warrant definite conclusions. However, 3 points are worthy of special note: (1) The number in whom impairment or improvement occurred is almost evenly balanced. (2) Even intensive treatment did not prevent a marked decrease in hearing in 2 patients with late syphilis. (3) The 2 cases with marked improvement had early meningeal neurosyphilis (neurorecurrence). That improvement in hearing may result from antisyphilitic treatment in this type of neurosyphilis has long been recognized (Benario, Moore). In our material there are 9 cases of neurorecurrence with "subnormal" hearing; the 2 cited above showed improvement, in 2 others the hearing remained stationary under adequate treatment, the other 5 did not return for a second audiometric examination. Thus our findings with respect to neurorecurrence may be regarded as confirmatory of the clinical impression.

The few data preclude conclusions as regards the effect of treatment on impaired vestibular reactions. Thirteen cases with "impaired" vestibular function and 7 with "normal" function showed no change throughout the period of observation. Two previously "impaired," improved; 2 with "normal" reactions to begin with, showed impairment later.

Memmesheimer and Theissing,[10] and especially Krassnig,[11] have reported favorable results following the use of malaria in patients with involvement of the 8th nerve, the improvement becoming evident a few months after the treatment. Many of their patients had congenital syphilis. Eleven of our 61 patients who had 2 or more hearing examinations received malaria inoculations in addition to intensive treatment with arsphenamin and bismuth. The hearing examinations made on the average of 24 months later showed no change in any case.

This report constitutes, so far as we know, the first in which an audiometer has been used in an effort to study the effect of treatment on hearing in syphilis. As in all studies of hearing, we are impressed by the discrepancies between the subjective impressions of the patients and the actual measurements of hearing acuity. Some individuals complain of deafness when none can be demonstrated. Others already deaf report improvement in hearing which when tested for is lacking. We believe, therefore, that the frequency with which favorable effects are obtained by treatment, as reported by earlier workers, is open to question. Further audiometric studies are needed.

With the exception of early meningeal neurosyphilis (including neurorecurrence), both of the methods of analysis which we have used in studying our material as to the effect of antisyphilitic treatment upon the hearing lead us to the conclusion that it has no effect either beneficial or detrimental.

Summary. 1. A statistical analysis has been made of the otologic findings in 286 patients with syphilis, special attention being given to the effects of antisyphilitic treatment on hearing. All cases have been excluded in which there was evidence of middle ear infection or in which it was clear that the hearing defect antedated the acquisition of syphilis. Hearing by air conduction was examined with a Western Electric Company 1–A audiometer.

2. Shortened bone conduction in the presence of good hearing has not been observed except in cases of high tone loss.

3. Vestibular reactions have been found diminished in about 50 per cent of the cases with marked impairment of hearing. In this material about 33 per cent of the cases with diminished vestibular reactions are not accompanied by impairment of hearing.

4. Involvement of the 8th nerve is apparently more often associated with neurosyphilis than with other forms of syphilis.

5. Evidence is given to show that a diagnosis of neurosyphilis based only on impaired function of the 8th nerve in a patient with syphilis is not justified.

6. Comparison of the amounts of antisyphilitic treatment received by the patients here observed warrants the conclusion that there is no relationship between treatment and the development of hearing defects.

7. Sixty-one patients were reëxamined otologically after an average period of 2 years; the hearing remained stationary in 52, improved in 4 and became worse in 5. The 2 showing most improvement both had early meningeal neurosyphilis (neurorecurrence); the 2 with greatest decrease had late syphilis.

8. With the exception of deafness associated with early meningeal neurosyphilis, it is concluded that antisyphilitic treatment has no effect on hearing, either beneficial or detrimental.

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CONJUGAL SYPHILIS—A STATISTICAL STUDY.

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In the natural course of events if one member of a married couple acquires syphilis the partner will become infected. In most instances this happens, but a certain proportion, larger than one ordinarily realizes, in some way escapes. Scant statistical data on conjugal syphilis is to be found in the literature. In fact, considering the large bulk of material bearing on syphilis, very little has appeared in this connection beyond interesting case reports.

Jordan,[1] reviewing 117 cases (husbands and wives), found that in 23 per cent syphilis was limited to the one first infected. He also felt that similar luetic manifestations in both were rare. It is stated by him that the one first infected is more inclined to neurosyphilis and that the one secondarily infected usually developed latent syphilis. Another finding was that if the one first infected did not have neurosyphilis the one secondarily infected was more liable to develop marked somatic syphilis. His opinion was that the treponema was attenuated during the development of neurosyphilis in the host. In his series he studied 100 cases (husbands and wives) in families where both partners were affected and found that 94 women were infected by their husbands and 6 husbands by their wives. Of the women, 72 developed active syphilis and 22 latent syphilis. The 6 men showed primary syphilis.

Kertesz[2] reported that in his series 50 per cent of the husbands of latent syphilitic wives showed treponema or treponematal elements in their spermatic fluid. Kertesz and Goldner[3] by intraocular injection of semen were able to produce syphilis in rabbits. The inoculum was obtained from patients with a history of syphilis and a negative serology or considerable treatment.

Dennie[4] felt that the age of the disease was the most important factor in its transmission. The older the infection the less danger of transmission existed. Physical examination showed evidence of the disease more frequently in the father than the mother. If marriage occurred during the first 5 years of the disease the woman ran a risk of infection. If the syphilis was of long standing in the father, the mother and children escaped.

Fournier[5] laid down certain conditions which should be fulfilled before permission to marry is granted. After some 50 years these rules are still applicable. Besides active treatment and clinical quiescence he emphasized the time element. Sir Jonathan Hutchinson[6] wrote, "Most authorities are agreed that, as a rule, patients who have reached the 6th year of their disease, although they may themselves be still liable to symptoms, do not transmit."

Galliot[7] was of the opinion that conjugal syphilis in the female was enough of a clinical entity to warrant a separate description. He found most frequently a form of latent syphilis with no symptoms other than positive serology or fetal accidents. To this he applied the term "forme fruste." Bertin[8] emphasized that this form of latent, often ignored, syphilis was of great importance because of the misfortune of hereditary syphilis. He also felt that prophylactic treatment should be given the contacts of these cases.

Payenneville[9] recommended that a husband or wife exposed to a syphilitic spouse be given a course of preventive treatment. He reported successful prophylaxis in 4 primary and 6 secondary cases and failure in 1 secondary case. Malherbe[10] reported a case in which the disease was transmitted from husband to wife during the initial incubation period. Levitin[11] mentioned a case of latent syphilis in a wife, the husband being free from infection. During the treatment of the wife the husband developed a penile chancre.

Pignet[12] recorded an instance of conjugal syphilis of the central nervous system with absence of mucocutaneous lesions in both husband and wife. He concluded that this bore out the neurotropic theory of Levaditi and Marie. Sezary,[13] however, felt that in conjugal neurosyphilis the law of coincidence, rather than a neurotropic organism, explains the nerve involvement. This form of syphilis is common and is bound to occur in both parties in a certain proportion of syphilitic marriages.

Hufschmitt[14] and Kloepfel[15] reported cases of conjugal syphilis in which the patients did not improve following the use of arsenicals, indicating to them an arsenic resistant strain of treponemata. Belgodere[16] cited 2 cases to show the vagaries of infection. One, a man, was exposed daily for 3 months to early syphilis in his mistress and failed to acquire the disease. The other, a woman, was infected by one illicit exposure.

Again quoting Sir Jonathan Hutchinson:[17] "There can be no duty more imperative, in the exercise of our profession, than that of abstaining from needlessly exciting in the minds of our patients suspicions as to conjugal purity."

When a married patient is admitted to our clinic, advice is given to bring in the spouse for a Wassermann test. This is not insisted upon too strongly nor is the other member questioned or instructed when appearing for the test. If the latter is positive the patient is registered for examination and treatment. If it is negative efforts are made to repeat the procedure at least twice. Incidentally the average dispensary patient is not anxious to bring in the spouse. Many of the negro patients registered as married are actually separated.

Study. In the syphilis treatment clinic of which I have charge in this hospital, an examination was made of 7896 records. Of this number, 4770 comprised married patients. Of these, both members

of the family were examined in 752 instances (376 husbands and wives). The husband alone was found to be infected in 60, the wife alone in 98, and both in 218 families. The interval between admissions of the two members of a family was interesting. It ranged from a few days to 8 years. In the instances of the longer intervals the spouse was admitted for some other condition and referred to the clinic because of a positive Wassermann test.

In considering the instances where both were infected the fact must be kept in mind that infection might have been acquired from sources other than conjugal. Many of these patients had latent syphilis, this was most common in the elderly negro. The initial lesion was disregarded, frequently called a "hair-cut," the secondary symptoms escaped notice, and the diagnosis was not made until the patient was admitted for some other reason and a routine Wassermann test made.

In only two instances did both husband and wife have neurosyphilis. It was felt that if a neurotropic strain of treponema existed a higher incidence of conjugal neurosyphilis would be present in this group. However, it must be remembered that most of these patients were negroes who develop somatic rather than neurosyphilis. In considering the type of syphilis as outlined in Table 4, one is led to the conclusion that individual resistance, rather than a strain of treponema, is probably the deciding factor.

In 41 per cent of this series one member escaped infection. It is felt that this is of importance because of the fear that has been generally disseminated concerning the infectivity of syphilis. The disease cannot be so extremely contagious, in the late stages, when a number approaching half of the husbands or wives in this group escaped. Also it would seem that the wife was less liable to transmit the infection since 38 more wives were syphilitic.

TABLE 1.—ANALYSIS OF MATERIAL.

Total records	7,896
Married	4,770
Single	3,126
Husband and wife examined	752
Both positive	436
Husband positive, wife negative	120
Husband negative, wife positive	196

TABLE 2.—THE TYPE OF SYPHILIS CONCERNED.

	Husband positive, wife negative.	Husband negative, wife positive.	Husband positive.	Wife positive.
Primary	7	1	22	2
Secondary	7	8	32	38
Latent	21	52	69	111
Tertiary	20	23	52	37
Congenital	1	9	0	4
Treated	4	5	20	9
Undetermined	0	0	23	17

In closing, a word of explanation concerning the tables. Table 1 shows the total records examined. Table 2 notes the types of syphilis in the entire series. Table 3 marks the interval between admission of patients. Table 4 shows the type of syphilis in the group with both infected. The term latent syphilis refers to those patients whose only symptom is a positive Wassermann test. The unclassified group are those who failed to register for examination.

TABLE 3.—THE INTERVAL BETWEEN ADMISSION FOR TREATMENT OF HUSBANDS AND WIVES.

	Husband positive, wife negative.	Husband negative, wife positive.	Husband positive, wife positive.
One week	25	57	55
One month	12	19	61
Three months	12	12	44
Six months	5	2	20
One year	2	4	7
Over one year	4	4	31

TABLE 4.—TYPE OF SYPHILITIC CONDITION WHEN BOTH HUSBANDS AND WIVES WERE INFECTED.

		Husbands										
				Syphilis tertiary								
		Syphilis primary	Syphilis secondary	Cardiovascular	Mucocutaneous	Central nervous system	Osseous	Visceral	Latent	Congenital	Treated	Undetermined
Wives	Syphilis primary	1	1	0	0	0	0	0	0	0	0	0
	Syphilis secondary	7	13	1	1	0	0	0	5	0	5	6
	Syphilis tertiary: Cardiovascular	0	0	2	2	0	0	1	1	0	1	0
	Syphilis tertiary: Mucocutaneous	2	0	0	1	0	0	0	5	0	0	1
	Syphilis tertiary: Central nervous system	0	0	2	0	2	1	1	2	0	1	2
	Syphilis tertiary: Osseous	0	1	0	0	0	0	0	2	0	1	2
	Syphilis tertiary: Visceral	0	1	0	0	0	0	0	2	0	0	1
	Latent	9	12	4	7	8	2	8	42	0	9	10
	Congenital	0	0	1	0	0	0	0	3	0	0	0
	Treated	1	1	1	0	0	0	0	2	0	3	1
	Undetermined	2	3	3	1	0	2	1	5	0	0	0

Summary. 1. There is presented an investigation of the records of 376 families in which syphilis was present in at least one member of the conjugal union.

2. Sixty husbands and 98 wives were syphilitic with non-syphilitic spouses.

3. In 218 families both husband and wife were syphilitic.

4. It is concluded that the type of syphilis depends upon the individual rather than upon any special strain of treponema.

5. Late syphilis is relatively non-infectious. Infectivity varies inversely with the duration of the disease.

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THE PROBABLE ALLERGIC NATURE OF CINCHOPHEN POISONING.

WITH SPECIAL REFERENCE TO THE ARTHUS PHENOMENON AND WITH PRECAUTIONS TO BE FOLLOWED IN CINCHOPHEN ADMINISTRATION.

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THE toxic nature of cinchophen is now fully recognized, but the fact that this drug was studied in numerous laboratories and extensively used clinically here and in Europe for nearly 15 years before the first case of serious poisoning involving the liver was reported (Worster-Drought[1]) emphasizes the need for a more thorough understanding concerning the mechanisms of drug action. The similarity between cinchophen poisoning and allergic reactions has been noted by various writers.[2, 3, 4] Recently Short and Bauer[5] summarized 41 cases showing allergic reactions from cinchophen

and its derivatives, and added 4 more. The prominent findings repeatedly noted are: the polymorphous character of the skin eruption, the occurrence of edema, the frequency of fever, and the occasional profound vasomotor disturbance.[3, 6] Exacerbation of joint pains[7] and gastro-intestinal disturbances[3] have also been reported. Leukopenia, lymphadenopathy, and eosinophilia have not been conspicuous findings. Significantly, the hypersensitivity to cinchophen appears to be acquired, and even in those cases in which a reaction occurs following the first dose, exposure to cinchophen previously in the form of proprietary antirheumatic mixtures is quite probable, as Short and Bauer have pointed out. The sensitivity to cinchophen appears to be specific; and as Davis[8] has shown, a patient sensitive to cinchophen may show no reaction to neocinchophen, although he is more apt to acquire such as sensitivity than a normal individual.

The Arthus Phenomenon. Probably the most serious and most dreaded reaction resulting from the injection of a foreign protein is the so-called Arthus phenomenon,[9] a severe localized sterile inflammatory process resulting in necrosis at the site of a subcutaneous injection of a protein to which the animal has been previously sensitized. Further studies have shown that this definition is too narrow in that the process may occur in other than subcutaneous tissue; it has been produced experimentally in the lungs,[10] kidney,[11] joints,[12] heart and pericardium,[13] brain,[14] submucosa of the stomach,[15] and liver.[16] The possibility of producing a sudden anaphylactic inflammation with possible necrosis in an organ like the liver is of utmost importance. Since cinchophen can produce all the other known allergic reactions, it is logical to accept the possibility that the acute yellow atrophy or necrosis which it produces may be a manifestation of the Arthus phenomenon, especially since many of the cases showed a previous allergic hypersensitivity. Particularly significant is the fact that severe hepatic damage has resulted from relatively small doses,[1] whereas large doses over long periods in non-sensitive patients apparently produce little if any liver pathology. There is furthermore suggestive evidence that cinchophen may affect other organs. Petty[17] reported a case in which a patient after taking 10 pastilles of cinchophen developed an acute pancreatitis with fat necrosis and hemorrhage. The absence of calculi in the pancreas and the normal appearance of the biliary system makes it appear highly probable that it was a spontaneous process. It is also interesting to find that Feer[18] reported the occurrence of agranulocytosis following the use of nirvanol, a drug known for its frequent allergic side reactions. These considerations do not imply that every case of acute yellow atrophy is the result of an allergic reaction, but they do emphasize the possibility that the visceral damages resulting from cinchophen and perhaps many other drugs may be the result of an allergic inflammatory process which apparently is akin to the Arthus phenomenon.

The difficulty of accepting the anaphylactic nature of drug reactions has been due in great measure to the fact that substances like cinchophen do not give in sensitized individuals skin tests, precipitin reactions, and the Prausnitz and Küstner reaction. This objection, however, is not valid, for these reactions are probably not due to cinchophen but to a metabolic derivative. The drug in the body immediately undergoes chemical changes, presumably oxidation to a hydroxy compound and conjugation with glucuronic acid, which is a carbohydrate derivative. The work of Heidelberger and Avery[19] and of Goebel and Avery[20] has emphasized the importance of carbohydrates as determinants in antigenic substances. It is probable that the real hapten may be a glucuronic acid-oxycinchophen. Attention must also be directed to the marked modifications in physiologic action resulting from alterations in the cinchophen molecule. The iodo-cinchophens and the salicylate compound, atophanyl, seem to be more dangerous than cinchophen, while neocinchophen appears to be less prone to cause side reactions. Only a proper coördination of chemical and immunologic research can solve the problem under discussion.

Precautions to be Observed. By tentatively accepting, however, the idea that side reactions are allergic, certain precautions and rules can be formulated:

1. Any drug which is thought to produce hypersensitivity should be given only if adequate and continual medical supervision is possible. The patient should be instructed to watch for untoward symptoms and be told to stop the drug at the first sign of hives, loss of appetite, nausea, headache, dizziness, or malaise.

2. The practice of giving large doses followed by a rest period should be abandoned, for this practice seems to favor the development of hypersensitivity. No advantage accrues from the routine of Graham[21] which consists in giving the drug for 4 days followed by a rest period of 4 days. The use of sodium bicarbonate does not apparently minimize the danger of cinchophen (Evans,[22] Rabinowitz[23]).

3. Cinchophen and similar drugs should not be given to patients with a history of asthma or hay fever, or who are hypersensitive to foreign proteins. It is especially interesting that patients sensitive to salicylates may ultimately become hypersensitive to cinchophen as is illustrated by the cases of Davis[8] and Rabinowitz.[23]

4. The simultaneous administration of cinchophen and of a foreign protein such as vaccines or milk parenterally should be avoided. The danger of this is demonstrated by Rabinowitz's[23] series of cases. Davis emphasizes the danger of giving iodids with cinchophen.

5. There is no justification for the intravenous injection of cinchophen or of its derivatives. Recently the writer has obtained evidence that the intravenous administration of even small amounts of sodium salicylate can produce a sensitivity that could not be effected by large doses orally.

6. Drugs producing side reactions should be given with caution to patients with damaged livers. One must confess that the idea stressed by most writer that previous liver damage sensitizes the liver to cinchophen is not borne out in the reported cases. Weis[24] emphasized that the 3 fatal cases which he studied had no history of liver or gall bladder disease, and others have made similar observations. Nevertheless, there is the theoretical danger, for the liver is concerned with detoxication mechanisms and probably with the synthesis of immunologic substances. Cinchophen and allied drugs should not be given if a depletion of liver glycogen is suspected; but it must be remembered that there is no convincing proof that a liver abundantly supplied with glycogen is resistant to injury from cinchophen.

The Treatment of Acute Yellow Atrophy. Since this condition is really a massive necrosis, as Beaver and Robertson[25] have pointed out, treatment must be directed first to counteract the shock and toxemia resulting from the absorption of necrotic tissue, and second to take care of the hepatic insufficiency resulting from the extensive destruction of parenchymatous tissue. If the patient can be tided over the crucial period, the chances of recovery are good, due to the great regenerative power of the liver. If the patient cannot retain food, glucose should be given parenterally. Small doses of insulin, 5 to 10 units 3 times a day, have been recommended by various writers. It may be tried, although the results of this treatment, as shown by various case reports, have been disappointing. If the blood sugar falls below 80 mg. the administration of glucose intravenously is indicated. Calcium in the form of calcium gluconate should be given intravenously or intramuscularly, and by mouth. While the evidence for the clinical value of calcium in this condition is still fragmentary, the rationale for its use is based on its protective and restorative action on the liver in carbon tetrachlorid poisoning,[26] and on the fact that calcium modifies allergic reactions. The use of liver extract as recommended by Bassler[27] should be included in the treatment. The diet should be very low in fat and also low in proteins, because of the loss of the deamination power of the liver. Skimmed milk and other milk products low in fat should be given, if tolerated, since milk is especially rich in calcium. Gelatin in the form of desserts should be given several times a day, for this food is easily assimilated and contains a high percentage of the amino acid, glycin. This compound is normally synthesized by the liver and is important in the detoxication processes and probably has other important physiologic functions. The use of sodium lactate has been advocated by Weigeldt,[28] but in view of the fact that the accumulation of lactic acid in the body occurs in certain metabolic dysfunctions involving the liver, this form of therapy seems distinctly illogical. The kidney condition, characterized by a marked albuminuria and nitrogen retention,

which is frequently observed in severe cases, is probably secondary to the liver damage, a form of renal hepatic syndrome similar to the one studied by Helweg and Schutz.[29] As a general rule it requires no special treatment. A number of authors have considered the possibility of surgical drainage in acute yellow atrophy, but there is not enough available data to draw any definite conclusions. It should be mentioned, however, that the case of acute pancreatitis reported by Petty[17] had surgical drainage of the pancreas and, in spite of the seriousness of the condition, the patient recovered.

Case Abstracts. CASE 1.—With a marked acute allergic attack. (Patient of Dr. S. Thompson.) A white woman, aged 36, developed an arthritis of the joints of her first toe. Guphen, a proprietary cinchophen derivative (the guaiacol ester of cinchophen), was given (1 tablet t. i. d. for 10 days). After a rest period of 10 days, the patient, because of the return of pain, took 1 tablet of guphen. About 30 minutes later she developed a sudden attack of palpitation, dyspnea, numbness and tingling of her extremities. There was edema about her eyes and the skin had a scarlet hue. Adrenalin eased her symptoms, and recovery occurred promptly. Skin tests of all articles of food eaten on that day as well as of guphen were negative.

The similarity of the clinical picture to foreign protein shock is evident. Sutton[6] and Barron[3] have described similar cases in which cinchophen was the cause of the profound vasomotor disturbance. The present case furnishes further evidence that no cinchophen derivative is entirely safe.

Atypical Cases of Cinchophen Poisoning. The present literature on cinchophen fails to emphasize that the drug may produce hepatitis without jaundice. If therefore it occurs concomitantly with another pathologic condition which may also produce liver damage, it may easily be overlooked. The following 2 cases will serve as possible illustrations.

CASE 2. (From the Surgical Service of Dr. F. W. Bancroft.)—Miss B., aged 60, has a history of asthma, hay fever, and symptoms of cholecystitis of many years' duration. Cholecystectomy and appendectomy, March 12, 1931. During the past year, she noticed brown pigmented areas over her intercostal angle and back. A few weeks before admission to the hospital, she developed dyspnea, nausea, cyanosis, and increasing weakness. On examination it was found that her heart was moderately enlarged, but gave no signs of valvular defects. Blood pressure: 158 systolic and 108 diastolic. The liver was markedly enlarged but not tender. The electrocardiogram showed a right axis deviation. Icteric index was 10.7. A test of liver function[30] was 46 per cent normal. Other laboratory findings were essentially normal. The condition was considered as cardiac failure with chronic passive congestion of the liver, until it was learned that the patient for the past year had begun taking neocinchophen instead of aspirin. Occasionally she took as many as 3 tablets daily, but the total amount was not large. Treatment consisted in giving calcium gluconate, and liver extract by mouth. A small amount of digitalis was also given. A high carbohydrate, low fat diet was prescribed. One month later her liver func-

tion as measured by the writer's test was 70 per cent of normal. Recently the patient's tolerance for fats has been definitely increased by feeding small amounts of bile salts. Clinical improvement has progressed very slowly.

Case 3. (From the Medical Service of Dr. C. F. Tenney.)—Mrs D., aged 32, a Puerto Rican, 2 years ago had a positive Wassermann reaction, which after 2 courses of antiluetic treatment (neoarsphenamin and bismuth) became negative. A miscarriage occurred 5 months ago. Two weeks before admission she developed a polyarthralgia, which was diagnosed as acute rheumatic fever, and cinchophen was prescribed (16 tablets in 6 days). She also received an intramuscular injection, but efforts to learn the nature of the agent injected were unsuccessful. Four days after stopping the medicine, she had a sharp pain in her left chest, pain and tenderness over her epigastrium, nausea and vomiting. At the time of her admission to the hospital, she was in a precomatose state. On examination, the sclera showed no icteric tinge, the heart was slightly enlarged to the left, the heart sounds lacked tonus, the second aortic was feeble, even though her blood pressure was 180/140. Scattered crackling râles were heard at the bases of her lungs, and a definite friction rub over the left anterior chest. The liver was greatly enlarged, extending below the umbilicus. It was soft and not tender. No ascites. Urine showed 4+ albumin, but no casts nor bile pigments. Blood chemistry: non-protein nitrogen 54 mg., uric acid 5.0 mg., creatinin 1.9 mg., sugar 125 mg. per 100 cc. of blood. Icteric index 7.5. Treatment consisted in daily hypodermoclysis of 5 per cent glucose until vomiting stopped, intramuscular injections of calcium gluconate, and of liver extract. One transfusion and several short-wave radio treatments were also given. The diet consisted mainly of milk, gelatin, and orange juice. Marked clinical improvement began on the 8th day; the heart sounds became normal; the blood pressure dropped to 146/108; the nausea subsided; and the temperature became normal.

There are good reasons for accepting that neocinchophen and cinchophen respectively were the immediate causes of the liver condition in the above cases. If the insidious nature of cinchophen poisoning had not been known, it is highly probable that other diagnoses would have been made, the first case as passive congestion due to cardiac failure, and the second case perhaps as luetic cirrhosis or atypical pneumonia. One can venture to predict that the first patient, had she continued to take neocinchophen, would have succumbed to the hepatitis. It appears that recovery in cinchophen poisoning is greatly retarded if any contributory cause of liver damage like cardiac failure or lues is present. These conditions undoubtedly impede the regenerative power of the liver.

Summary. The probable allergic nature of cinchophen poisoning is discussed and the hypothesis is presented that the acute yellow atrophy caused by this drug may perhaps represent a special form of the Arthus phenomenon.

Precautions in the use of drugs known to produce side reactions are outlined and treatment of acute yellow atrophy is described.

A case of an acute allergic reaction (from guphen) and 2 cases of atypical cinchophen poisoning with hepatitis but no jaundice are presented.

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NEVUS FLAMMEUS NUCHÆ; ITS OCCURRENCE AND ABNORMALITIES.

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One of the commonest congenital defects of the skin is the variety of flat angioma known as nevus flammeus nuchæ. Interest in this minor deviation from the normal was induced by encountering a number of superimposed skin conditions which had apparently developed at some later period than that when the nevus had originally been noted.

The appearance of the unaltered angioma varies in size, depth of color and type of configuration but seldom is there much change in the location. This usually adheres strictly to the region on either

side of the posterior midline and is fairly symmetrical in outline. In the majority of cases it is entirely included in a cephalo-caudal dimension between the occipital protuberance (inion) and the tip of the spine of the 5th cervical vertebra. The long axis of the appearance is usually up and down. Frequently one is somewhat confused in the classification of these cases by instances of mottling produced by vitiligo, old sunburn, scars, and the hypertrophic weather-beaten skin of the aged. Faint pinkish marks may mean a trivial degree of the condition. Pressure is frequently of distinct use in ruling out these somewhat suggestive appearances and none were included in the list as positive findings if there was any doubt as to their true nature. A geographical type of broken-up, jutting, indented and, in a small degree, marginal insular configuration is the rule. Seldom is the area of the nevus of a compact form; usually the edges are lacy. Frequently there is a marked similarity to the blot produced by gently pressing a folded paper with an ink-drop in the crease and then opening it flat again. Elevation is not found in this form under discussion; its presence automatically removes the case into another vascular category. The color varies from light pink to a purplish red. Often it corresponds fairly accurately to the natural color of the lips of the subject. The frequency of occurrence in the adult has been inquired into and would appear to be greater than its incidence in the newborn although my impression formerly had been somewhat the reverse. The well-known fact that many angiomata appear some time after birth may have its bearing in this connection.

In a group of medical students, out of 275 individuals examined, typical nuchal nevi were found in 13 instances (4.7 per cent). In a skin dispensary, 100 adult patients, 50 consecutive of each sex gave a count of 8 (4 in each sex). Of 175 casual examinations 10 had nevi (5.7 per cent). On the other hand, 210 babies, routinely examined the day after birth in a maternity nursery showed but 6 to have a nevus at the back of the neck (2.8 per cent) though there was numerous such appearances elsewhere, notably the eyelids. The percentage in the adult cases showing the mark was 5.6. Grouping these 760 cases without respect to age the incidence of this condition was found to be 4.8 per cent, a very considerable proportion of mankind and probably an underestimation of the actual figures if intermediate ages were included. Search of the literature of the past 15 years gives no reference to the condition.

The mark is, of course, most readily apparent in males and in severely bobbed females but the matter of sex does not appear to affect the incidence of the condition. The practice of wearing the hair long, however, does seem to alter the mark and indirectly induce changes in the abnormal skin of that region. The hair of the affected region appears to be uninfluenced by the mark and grows normally, hiding the defect unless it is kept in a close clipped condition. Of 8 individuals not included in the above figures, con-

sulting me for skin outbreaks overlying nuchal nevi, 7 were women. Of these, 5 had long hair worn in a knot at the back of the head at least some part of each day. All of the 5 were over 40 years of age. In all of the 8 cases cited there was at one time or another, during my observation of the case, a clear diagnosis of a nuchal nevus serving as a base for the more recent outbreak.

Case Abstracts. Case 1.—C. W. F., a white man, aged 52 years, an insurance agent, consulted me March 23, 1931 on account of a small swelling which had occurred at the edge of an old birthmark, a port wine stain in the midline of the back of the head just above the posterior hair line. The mark was of a purplish color and the elevation somewhat of a darker shade

Fig. 1.—Typical nuchal nevus.

and the size of a grain of wheat. He had noticed its presence for several weeks. Permission for a biopsy was refused so, after preliminary radiation by Roentgen rays, which only caused slight flattening of the growth, it was destroyed by electrodesiccation under novocain anesthesia. The growth was solid and firm and after destruction left a smooth scar. In November of the same year a similar appearance was noted about an inch (2.5 cm.) from the old scar and also situated on the angiomatous base. It was treated in a similar fashion. In the course of the next year, 1932, two more areas distinct from either of the former sites became elevated and were treated with radium, causing them to flatten down and separate as scales leaving some underlying infiltration which was fulgurated. No more lesions of this type have been seen to date (June, 1933) though a few pustules were apparent on the normal skin around the nevus in September, 1932. These were follicular infections and discharged their contents.

Cases 2 and 3.—F. C., a white school girl aged 11 years, was brought to the office for a crusted eruption at the back of the neck within the hairy area. It had existed off and on for several years and was quite itchy. No pediculosis was present and but a moderate amount of seborrhea. Under treatment there was a rapid improvement and disappearance of the crust with the emergence of an underlying nævus flammeus heretofore masked by the dermatitis.

The mother, Mrs. W. D. C., aged 41 years, had an identical mark in that situation with some scaliness and itching. There were a few areas of seborrheic dermatitis in her scalp. She had been told from childhood that she had a strawberry mark at the back of her head. (Another daughter [sister to F. C.] had a large pigmented and hairy nevus on the outer side of her left lower leg). Hairpins were used in a knot covering the nevus and sometimes were employed to scratch the scaly area.

CASE 4.—Mrs. S. B. W., a white woman aged 65 years, had had "eczema" at the back of her head for years; 20 at least. Examination showed an irregular but marginated patch in the hairy area in the midline, spreading symmetrically on both sides. It measured 2 inches up and down and 1½ inches across at its greatest extent. Some crusts were apparent on the surface and superficial excoriations. After 2 weeks' treatment the superficial inflammation had subsided and there was plainly apparent a typical nuchal nevus. A knot secured by composition (sometimes metallic) hairpins covered the very area affected. Roentgen ray, in dosage insufficient to cause epilation, was most beneficial in causing a subsidence of the eruption.

CASE 5.—F. L., an unmarried white woman, aged 53 years, had had an irritated area at the back of the scalp for several years. Her hair was kept short partly on this account as she found that long hair heated the patch and increased itching. The area resembled psoriasis somewhat, though there were no other evidences of that disease on any other part of the body. Roentgen ray and a tar lotion caused a disappearance of the scale and allowed one to identify a port wine mark in that region, previously masked by the exfoliation. Heretofore its redness had been thought to be due to the inflammatory base of the outbreak.

CASE 6.—Mrs. C. M. H., aged 52 years, white, had suffered from scalp irritation for a number of years. There was a distinct nuchal nevus with, in places, a scaly eczematoid eruption overlying it. In addition a seborrheic dermatitis was present over the right ear. No appearance of psoriasis was to be noted on the body, and the scalp outbreak was in no wise indicative of that disease. The birthmark had been present from early childhood, she had been told. Her hair, while thin, was long and knotted in the back with metal hairpins.

CASE 7.—Mrs. A. K., aged 48 years, was practically identical with that preceding in all respects save that seborrheic dermatitis elsewhere was not present.

CASE 8.—Mrs. M. N., white, aged 62 years, came for relief from a sharply marginated seborrheic dermatitis affecting the scalp, neck and postauricular areas. In the latter region there was oozing and crusting, elsewhere the outbreak was a sheet of dull red with a thin, crackled, brownish-yellow scale on the surface. The history was definite as to the presence of a "strawberry mark from childhood" with the added eruption appearing on its surface 2 years ago and spreading centrifugally to its present dimensions.

Summary. 1. From examination of 760 individuals it would appear that nuchal nevi occur in about 5 per cent of the population and are to be noted more frequently in the adult (5.6 per cent) than in the newborn (2.8 per cent).

2. While the impression exists that the two sexes are about equally affected by the nevus, it served as a starting point for inflammatory outbreaks mainly in long-haired individuals, the short-haired being for the most part unaware of its existence. Hairpins may have had some influence in the production of secondary irritation.

3. The usual outbreak on this abnormal skin is of the nature of a dermatitis, seborrheic or eczematoid, with an occasional resemblance to psoriasis.

REVIEWS.

PATHOGENIC MICROÖRGANISMS. By WILLIAM HALLOCK PARK, M.D., Professor of Bacteriology and Hygiene, University and Bellevue Hospital Medical College, and Director of the Bureau of Laboratories of the Department of Health, New York City; and ANNA WESSELS WILLIAMS, M.D., Assistant Director of the Bureau of Laboratories of the Department of Health, New York City. Pp. 867; 215 engravings and 11 full-page plates. Tenth edition, enlarged and thoroughly revised. Philadelphia: Lea & Febiger, 1933. Price, $7.00.

"OUR experiences to date with active immunization against diphtheria and scarlet fever are given. . . . The recent additions to our knowledge of yellow fever, poliomyelitis, bacteriophage, undulant fever, etc., have received due attention. . . . The comprehensive summary table has been continued and revised, since many have continued to express appreciation of it. This table gives the essential characters of and pathologic conditions caused by each of the commoner bacteria. . . . The bibliography has been added to." (From Authors' Preface.)

THE BIOLOGY OF THE PROTOZOA. By GARY N. CALKINS, PH.D., SC.D., Professor of Protozoölogy, Columbia University. Pp. 607; 223 illustrations, and 2 colored plates. Second edition, thoroughly revised. Philadelphia: Lea & Febiger, 1933. Price, $7.50.

THE author maintains much the same style of presentation as in the first edition. More important changes consist in omitting discussion of chlorophyll-forming flagellates, and the addition of a chapter on parasitic protozoa. The latter is incomplete and uncritical. There also has been extensive rearrangement of other subject matter, and revision of taxonomy.

H. R.

STARLING'S PRINCIPLES OF HUMAN PHYSIOLOGY. Edited and revised by C. LOVATT EVANS, D.SC., F.R.C.P., F.R.S., Jodrell Professor of Physiology, University College, London. The chapters on The Central Nervous System and Sense Organs revised by H. HARTRIDGE, M.A., M.D., SC.D., F.R.S., Professor of Physiology at St. Bartholomew's Medical College. Sixth edition. Pp. 1122; 562 illustrations, 10 in color. Philadelphia: Lea & Febiger, 1933. Price, $8.75.

THE extensive use of this book since its first appearance, in 1912, has proved its high merit as a textbook for medical students and for those who are specializing in physiology. Since Starling's death, the two revisions by the present editor, who occupies the chair previously held by Starling, have increased its usefulness as a textbook and book of reference in this rapidly changing field of science. This latest (6th) edition, appearing three years after the 5th, contains notable improvements, in textual revision, discussions of very recent experimental work, and addition of many new illustrations. A new feature is the notation of specific references, which makes it possible to locate more easily the sources of statements made; and, because of the discrimination in the selection of this bibliography, guides the reader to the more important contributions in current literature.

I. Z.

A German Doctor at the Front (Die Front Der Arzte). By Professor Dr. Wilhelm His; translated from the original German by Col. Gustavus M. Blech, Medical Corps, Reserve, and Brig. Gen. Jefferson R. Kean, Medical Corps, U. S. A. (Retired). Pp. 230; 1 illustration. Washington, D. C.: The National Publishing Company, 1933 (American edition). Price, $2.50.

Although the distinguished author of these reminiscences states that their purpose is rather to draw useful lessons from his war experiences than to entertain, they provide much of interest in both directions to anyone desirous of knowing how the other half lived while the fire curtain was down. The Swiss son of an eminent Swiss anatomist many years professor at Leipsic, the younger His became a naturalized German citizen in 1906, and was professor of internal medicine at the Charité, Berlin, when the war broke out. Volunteering early, he saw active service on both Eastern and Western Fronts, in Turkey, Mesopotamia, Persia, Palestine and the Ukraine. His cosmopolitanism adds color to the narrative and authority to such reasoned optimism as that the World War should be regarded, not as the greatest of human catastrophes, but as the greatest of human experiences. The tenacity displayed by all sides is sufficient evidence to him that the civilized world, far from degenerating, may have found in the teachings of the war the kernel of their future happiness. To one who, like the Reviewer, cut his investigative teeth on the bundle of His, if such a barbarism may be permitted, this work appeals with special emphasis. That it should be translated and promoted by two medical officers of the U. S. Army is but another demonstration that good fighters or even good hating fighters are not apt to continue the fight or hate after the quarrel is over. E. K.

History and Source Book of Orthopædic Surgery. By Edgar M. Bick, M.A., M.D., Adjunct Orthopædic Surgeon, Hospital for Joint Diseases, New York City; Adjunct Orthopædic Surgeon, Montefiore Hospital, etc. Pp. 254; illustrated. New York: The Hospital for Joint Diseases, 1933. Price, $1.50.

The Hospital for Joint Diseases is to be commended for this demonstration of its breadth of purpose and congratulated in these times of enforced economies on its successful adaptation of the photographic format of book-making in lieu of the more expensive printing. We heartily agree also with Dr. Brackett's introductory remarks on the pleasure and profit of sometimes going back to the past, in order to examine the steps in our progress to our present position and to praise famous men. The author has followed the chronologic approach for the first 5 chapters; and in the next 6 considered the modern period from the points of view of physiology, pathology, methods of practice in bone, joint and muscle-tendon surgery, non-operative orthopedics, with a final chapter on the rise of orthopedic hospitals and institutions. E. K.

Lymphatics, Lymph and Tissue Fluid. By Cecil K. Drinker, B.S., M.D., Professor of Physiology, Harvard School of Public Health, and Madeleine E. Field, A.B., Ph.D., Instructor in Physiology, Harvard School of Public Health. Pp. 254; 11 illustrations and various tables. Baltimore: The Williams & Wilkins Company, 1933. Price, $3.00.

This is an interesting and even entertaining monograph on the physiology of lymph and lymphatics. The authors bring good experimental knowledge and acquaintance with the literature which, combined with a real gift for writing, has produced a valuable review. The chief subjects covered are

the structure and permeability of lymphatics, the permeability of blood capillaries, the composition of lymph and the flow of lymph in health and disease. Many controversial points arise, for example, the effect of inflammation on the flow of lymph; on these points the authors, while presenting all points of view, state their own opinions freely. There is a well-arranged bibliography. M. McC.

HUMAN VALUES IN PSYCHOLOGICAL MEDICINE. By C. P. BLACKER, M.C., M.A., M.D., M.R.C.P. Pp. 179. New York: Oxford University Press, 1933. Price, $2.50.

THE purpose of this book is to elaborate in the field of medical psychology further material regarding concepts of values as related to the life, personal characteristics and idiosyncrasies of the psychiatric patient. Secondarily, an attempt is made to relate the principles of psychologic medicine to those of biology. The book attempts to link philosophy to medical psychology, with special reference to psychoanalysis and occasionally to the practice of psychiatry. The concept of values as experienced by the individual is elaborated with emphasis on the idiosyncrasies individuals possess rather than their similarities to others.

Chapter IX, on the productive, the transmissive and the reactive conceptions of value, summarizes most of the material of the book and gives it its closest tie-up with clinical psychiatry. The last chapter, "Life and Death Instincts," bears little relation to the rest of the book. Here the author cleverly attempts to refute Freud's discussions on the death instinct, though his grounds will not be accepted by orthodox Freudians.

The book is of value to those who are interested in the theoretical aspects of psychiatry and psychologic medicine. It has no practical clinical value. L. S.

PARALYSIS IN CHILDREN. By R. G. GORDON, M.D., D.Sc., F.R.C.P. (ED.), Physician, Bath and Wessex Orthopaedic Hospital; Physician, Royal United Hospital, Bath, etc., and M. FORRESTER BROWN, M.D., M.S. (LOND.), Surgeon, Bath and Wessex Orthopaedic Hospital; Surgeon to County Orthopaedic Clinics, Wiltshire, Somerset, and Dorset. Pp. 328; 116 illustrations. New York: Oxford University Press, 1933. Price, $4.50.

WHILE not broad in its scope, this work concerns itself with that borderland where neurology and orthopedics meet.

The subject-matter is considered under three headings: General, including the physiology of movements, the incidence of lesions, the causes of paralysis and the diagnostic significance of physical signs. Clinical, illustrating the various syndromes by cases and showing the difficulties in diagnosis and treatment. Treatment, giving in detail the physiotherapy and non-operative orthopedics.

The book is abundantly and aptly illustrated and will prove very helpful to those interested in paralytic children. N. Y.

A SYNOPSIS OF SURGERY. By ERNEST W. HEY GROVES, M.S., M.D., B.Sc. (LOND.), F.R.C.S. (ENG.), Consulting Surgeon to the Bristol General Hospital; Emeritus Professor of Surgery, Bristol University. Pp. 693; 64 illustrations, 13 colored plates. Tenth edition. New York: William Wood & Company, 1933. Price, $5.00.

THIS well-known work has been revised to include the newer knowledge of the surgery of the sympathetic nervous system and the Orr treatment

of compound fractures and osteomyelitis. A new chapter, wherein the principles of amputations are outlined, has been added, which presents this material in one section rather than scattered through the book as in previous editions. These subjects have been dealt with, as have all other topics in the book, in brief abstract form.

The conciseness of this work requires that it be dogmatic in its presentation. As an outline of Rose and Carless' *Manual of Surgery*, it presents the salient facts presented there. One can no more obtain the same perspective from an outline as from the original than one can from a rough sketch as from a finished painting. To those studying surgery for the first time, this book, like "a little knowledge," is dangerous. To the individual who has a thorough knowledge of surgical literature, this book will be useful for refreshing the memory for facts forgotten. For the student who hopes to cut short hours of study, it will afford a skeleton of information, but here too it should be used only as should lecture notes. I. R.

THE TECHNIQUE OF LOCAL ANESTHESIA. By ARTHUR E. HERTZLER, A.M., M.D., PH.D., LL.D., F.A.C.S., Professor of Surgery, University of Kansas; Surgeon to the Halstead Hospital, Halstead, Kansas, and to to St. Luke's Hospital and St. Mary's Hospital, Kansas City, Mo., and to the Providence Hospital, Kansas City, Kansas. Pp. 292; 148 illustrations. Fifth edition. St. Louis: The C. V. Mosby Company, 1933. Price, $5.00.

THE fifth edition of Hertzler's monograph follows the same outline that has been used in previous editions. After preliminary discussion of the drugs and their actions, he discusses the technique of anesthesia according to the anatomic position in the body. Neuroanatomy of each region is briefly reviewed, followed by a description of the technique of placing the anesthetic solution. A new section on spinal anesthesia has been written by Dr. A. E. Spelman, and a short chapter on intravenous anesthesia, using the barbiturates, has been added by Dr. Raymond F. Gard. The book contains many drawings and photographs illustrating the techniques discussed. There are several notable omissions, for instance, paravertebral anesthesia in angina pectoris. The book fills a place as a reference work for those who wish to learn the technique of local anesthesia.

L. F.

THE OPERATIVE STORY OF CLEFT PALATE. By GEORGE MORRIS DORRANCE, M.D., F.A.C.S., Professor of Maxillofacial Surgery, The Thomas W. Evans Museum and Dental Institute School of Dentistry, University of Pennsylvania; Surgeon to St. Agnes' Hospital and to the American Oncologic Hospital, Philadelphia. Assisted by ENAYAT SHIRAZY, D.D.S. Pp. 564; 534 illustrations. Philadelphia: W. B. Saunders Company, 1933. Price, $6.50.

FROM a historical point of view the author and his assistant have, by collecting the data which are presented in this volume, done a monumental piece of work. The book is what it is designated, "The Operative Story of Cleft Palate." From this standpoint it will make an excellent reference work.

Throughout the historical sections of the work, however, the reportorial style has been used, and no attempt has been made to collate the material in an easy biographic sequence. Quotation marks are used as on page 1, in discussing Celsus, with no reference as to the author quoted. Sentence construction is often stilted, and more than once grammatically incorrect. In the preface, "Dr. Joseph Sweet" should have been Dr. Joshua Sweet, and "Muetter Museum" on page 371 should have been Mütter Museum.

There are numerous evidences of this sort which suggest a laxity in proofreading.

The illustrations must be discussed from two angles. Those collected from the literature for which the author has no responsibility except for their selection. Many of these are of great historical interest. The Reviewer does, however, believe that many of the collected illustrations may have been omitted. The illustrations which the author presents as original are of unusual excellence.

The final chapters of the book which deal with the Applied Anatomy and Pathology of Split Palate, The Occurrence and Distribution of Split Palate, the chapters on the Operative Treatment of Cleft Palate and the one on Conclusions are written in a much better style. In the operative field, the author has made valuable contributions, and he has given a clear description of his "push-back" operation. The chapter on The Rôle of Speech in Split Palate Patients covers a scant $2\frac{1}{2}$ pages. The subject is too important to have been given so little space. The bibliography covers 87 pages and is the most complete yet published.

This book will prove a valuable reference book for surgeons and medical historians. I. R.

SURGERY OF THE STOMACH AND DUODENUM. By J. SHELTON HORSLEY, M.D., F.A.C.S., LL.D., Attending Surgeon, St. Elizabeth's Hospital, Richmond, Va. Pp. 260; 136 illustrations. St. Louis: The C. V. Mosby Company, 1933. Price, $7.50.

THIS delightfully written monograph was dedicated by the author "To my Colleague and Rival, Stuart McGuire, Gentleman, Master Surgeon." On the Reviewer always falls the task of expressing himself as to whether a given work is merely just another volume to review or whether the work is a distinct addition to the literature of the subject. It was, indeed, a pleasure to have been privileged to review this monograph which unquestionably falls in the latter class. In the short space of 260 pages, including the index, the author has succeeded in covering the embryology, anatomy and physiology of the stomach and duodenum, the diagnosis of lesions of these viscera, the preliminary preparation, anesthesia, incisions and after treatment. The illustrations, most of which are new, are well chosen and skilfully executed. The selection of the material presented has been done thoroughly, and, while one may occasionally not agree with every statement, there is behind them a wealth of clinical experience. The author has long been known as a surgeon who realizes the importance of function in the rehabilitation of patients with lesions of the stomach and duodenum, and in this volume he has time and time again referred to the necessity of the surgeon considering the physiology of this area if he is to obtain the best possible results. If the Reviewer does not interpret the work incorrectly, this monograph will soon become a standard by which subsequent volumes dealing with this subject will be judged. I. R.

THE ENLARGED PROSTATE AND PROSTATIC OBSTRUCTION. By KENNETH M. WALKER, F.R.C.S., M.A., M.B., B.C., Jacksonian Prizeman and Hunterian Professor, Royal College of Surgeons, 1911, 1922, 1924, 1933; Lecturer in Venereal Diseases, St. Bartholomew's Hospital, etc. Pp. 223; 63 illustrations, 1 colored. Second edition. New York: Oxford University Press, 1933. Price, $4.25.

A REEDITING of the 1926 publication was to be expected because of the recent important advances in therapy. The book keeps its attractive small size and is better printed than before. New chapters on Mechanism of Obstruction and The Malignant Prostate are incorporated. That on

Obstruction at the Bladder Neck is rewritten *in toto* to distinct advantage over the older edition, while the chapter on Per-urethral Operations is brought up to date by the addition of prostatic resection, on which the author is one of the recognized authorities in Great Britain. It is to be commended again for its concise presentation and sound judgment.

A. R.

St. George's, 1733–1933. By J. Blomfield, O.B.E., M.D. Pp. 120; illustrated. London: The Medici Society, 1933. Price, 5s.

The history of this important London hospital and medical school (the latter established a century later), which for 200 years has occupied its present site at Hyde Park Corner, is adequately covered in this compact little volume. Chapters for each half century of its existence, with lists of governors who have filled the office of treasurer, physicians and surgeons and their assistants, from 1733 on, complete the volume. It is perhaps significant of the continued dominance of the clinical side in London medical schools, that a consulting and honorary bacteriologist (both appointed in April, 1913) are the only non-clinical names included. John Hunter, of course, frequently appears in the earlier pages, while such familiar names as Abernethy, Acland, Allbutt, Askew, Baillie, Charles Bell, Brodie, Burdon-Sanderson, Cheselden, Michael Foster, Gull, Heberden, Home, Manson, Humphry Rolleston and Thomas Young remind us of the distinguished position that this institution has always occupied. E. K.

Histopathology of the Peripheral and Central Nervous System. By George B. Hassin, M.D., Professor of Neurology, University of Illinois, College of Medicine, and Attending Neurologist, Cook County Hospital, Chicago. Pp. 491; 229 illustrations. Baltimore: William Wood & Co., 1933. Price, $6.00.

Hassin's new work is the third text on neuropathology to be published in this country within the present year. It is a systematic description of the pathologic changes which may occur in the peripheral nerves, the spinal cord and the brain. The author has wisely refrained from extensive discussions of clinical features, since there are available a number of excellent books on clinical neurology. Nor is there to be found in this work a discussion of general pathology, for such concepts as inflammation, degeneration, trauma and tumor growth are well treated in our several modern textbooks on pathology. The book is concise and in fact as well as in name covers the subject matter indicated by the title. The illustrations are excellent. The book itself clearly reflects the long and distinguished career of the author in the field of neuropathology. The Reviewer would invite particular attention to the final chapters wherein is given a outline of the staining methods that are used in Hassin's laboratory. B. L.

Some Modern Extensions of Beaumont's Studies on Alexis St. Martin. Beaumont Foundation Lectures. By W. B. Cannon, M.D., S.D. LL.D., George Higginson Professor of Physiology, Harvard Medical School; Beaumont Lecturer for 1933. Pp. 87. Detroit: Lectureship Foundation Committee of the Wayne County Medical Society, 1933.

The twelfth series of lectures on this foundation coincide with the centennial of Beaumont's great work on the gastric juice. It is especially appropriate they should be given by one who is so well able to present recent important advances that are connected with the work of our pioneer physiologist. Beaumont's correct and false views on hunger and thirst, relations of digestion to health, and digestive disturbances produced by pain and emotional excitement are well reviewed and elaborated in the light of present knowledge. E. K.

YOUR LONG-SUFFERING STOMACH. By ARTHUR F. KRAETZER, M.D. Pp. 120; illustrated. New York: Robert M. McBride & Co., 1933. Price, $1.50.

THE author has crisply condensed much sound information on nutrition within the span of nine chapters. His advice to diners may be summarized in the Socratic phrase "nothing too much." There is little of the partisan in him and his common sense views should prove a timely antidote to the prevailing dietary fads. As a book primarily for laymen, it is properly somewhat arbitrary on points which, strictly speaking, may still be considered debatable. Finally, as is essential in this type of book, there is wit enough to season the more technical portions for the casual reader.

W. A.

SPONTANEOUS PNEUMOTHORAX IN THE APPARENTLY HEALTHY. By HANS KJAERGAARD. Pp. 251; 29 illustrations. Copenhagen: Levin & Munksgaard, 1932. (Translated from the Danish by Hans Andersen, M.D., Copenhagen.)

ON the basis of 51 cases coming under his own scrutiny, and some 200 cases reported in the literature, the author concludes that spontaneous pneumothorax in the apparently healthy is a distinct clinical entity, for which he suggests the term pneumothorax simplex. It includes all cases of spontaneous pneumothorax occurring without demonstrable cause in healthy persons without demonstrable tuberculosis, and running an afebrile course without any, or with at most trifling, pleural effusion. Due to the rupture of a valve vesicle on the surface of the lung, a vesicle arising either near a scar of a small healed tuberculous process or through local emphysematous changes without scar tissue, the condition may be assumed to have nothing to do with active tuberculosis and the patients should be spared unnecessary treatment for, and fear of, tuberculosis. The evidence presented is clear-cut and convincing.

R. K.

DISEASES OF THE NERVOUS SYSTEM. By W. RUSSELL BRAIN, M.A., D.M. (OXON.), F.R.C.P. (LOND.), Assistant Physician to the London Hospital and the Royal London Ophthalmic Hospital; Physician to the Hospital for Epilepsy and Paralysis, Maida Vale. Pp. 899; 50 illustrations. New York: Oxford University Press, 1933. Price, $8.75.

SOME deviation is here shown from the conventional arrangement of this branch of medicine. Opening with a rather lengthy discussion of the anatomy and physiology, as applied to the interpretation of the physical signs of nervous diseases, the further consideration of these branches appears later as introductions to the clinical sections.

Encephalitis lethargica and intracranial tumors are treated in the full light of modern research. The much neglected subject of fibrositis is considered. The value of fixation of the muscles in Bell's palsy is recognized, though not in its most approved form. The immediate and late effects of head traumata are fully discussed. The importance of the recently discovered metabolic centers in the hypothalamus is carefully considered, including their relation to general medicine, and a new chapter appears, entitled: Diseases of the Nervous System in Relation to Life Insurance. No preference is shown for the various conflicting theories concerned with psychopathology, the reader being referred to the original works of such authors. Intelligence tests—and these should include survey of the emotional realm—have been relinquished to psychiatry, but both departments of neuropsychiatry are still claiming the psychoneuroses.

One finds here the recent advances, thus giving the most comprehensive neurology that has yet appeared in English, and its popularity is predicted. The subject matter is followed by an excellent reference list and index.

N. Y.

HEALTH AND ENVIRONMENT. (Recent Social Trends Monograph.) By EDGAR SYDENSTRICKER. Pp. 217; 50 illustrations. New York: McGraw-Hill Book Company, 1933. Price, $2.50.

ONE of the series of monographs resulting from the work of President Hoover's Research Committee on Social Trends, this book endeavors to cover the whole field of health and disease in relation to geographic factors, city and country, economic and social status and occupation, without forgetting the known influence of heredity. Mortality trends—both in their civic and genetic aspects—each receive separate chapter treatment. Necessarily concerned chiefly with statistical analysis, the book is of value rather as a permanent collection of important data than for casual light reading.

E. K.

LECTURES ON THE HISTORY OF MEDICINE, 1926–1932 (MAYO FOUNDATION LECTURES). Pp. 516; 26 illustrations. Philadelphia: W. B. Saunders Company, 1933. Price, $5.00.

HEREIN is produced a series of 18 lectures under the auspices of The Mayo Foundation and several midwest universities. As explained by Dr. Louis Wilson, in the Introduction, "No attempt was made to cover the entire field of medicine nor to present the topics in any logical sequence. Men of learning were invited to come at their own convenience and to talk on historical topics of their own selection." The topics naturally cover a wide range. The Physiology of Respiration, Pathology, Resurrection Days, Billings, Paré, First American Journals, Warthin's Physician of the Dance of Death and so on, by such well-known writers as Sewall, Coupal, Seelig, Garrison, Packard, Corner and others. The book should furnish many pleasant evenings to the literary minded and we are glad to note that there will be more to come.

E. K.

BOOKS RECEIVED.

NEW BOOKS.

Metabolic Diseases and Their Treatment. By DR. ERICH GRAFE, Professor of Medicine and Director of the Clinic of Medicine and Neurology at the University of Würzburg, Germany. Translated by MARGARET GALT BOISE, under the supervision of EUGENE F. DUBOIS, M.D., Medical Director, Russell Sage Institute of Pathology, and Professor of Medicine, Cornell University Medical College; and HENRY B. RICHARDSON, M.D., Associate Professor of Medicine, Cornell University Medical College. Pp. 551; 37 illustrations. Philadelphia: Lea & Febiger, 1933. Price, $6.50.

Industrial Health Service. By LEVERETT DALE BRISTOL, M.D., DR.P.H., Health Director, American Telephone and Telegraph Company, New York City; formerly Commissioner of Health of the State of Maine, and Professor of Preventive Medicine and Public Health, University of Minnesota. Pp. 170. Philadelphia: Lea & Febiger, 1933. Price, $2.00.

Histology. By S. RAMON-CAJAL, M.D. (MADRID), F.R.S. (LONDON), LL.D. (CLARKE), Director, Royal Cajal Institute for Medical Research; Emeritus Professor of Pathology, University of Madrid Faculty of Medicine; Novel Premiate in Medicine; Life Senator of Spain. Revised by J. F. TELLO-MUÑOZ, M.D. (MADRID), Professor of Pathology, University of Madrid Faculty of Medicine. Authorized translation from the tenth Spanish edition by M. FERNAN-NUÑEZ, M.D. (MADRID), Professor of Pathology, Marquette University Medical School. Pp. 738; 535 illustrations. Baltimore: William Wood & Company, 1933. Price, $8.00.

Red Blood Cell Diameters. By CECIL PRICE-JONES, M.B. (LOND.). Pp. 82; 44 illustrations. New York: Oxford University Press, 1933. Price, $3.50.

Diet and Dental Health. By MILTON T. HANKE. Pp. 236; several illustrations; 21 graphs and 42 plates, mostly colored. Chicago: The University of Chicago Press, 1933. Price, $4.00.

Lectures on the History of Medicine, 1926–1932 (*The Mayo Foundation Lectures*). Pp. 516; 26 illustrations. Philadelphia: W. B. Saunders Company, 1933. Price, $5.00.

Verhandlungen der Deutschen Gesellschaft für Kreislaufforschung. VI. Tagung. Gehalten zu Würzburg am 6. und 7. März 1933. By PROF. DR. BRUNO KISCH, Cologne. Pp. 276; 97 illustrations and 35 tables. Leipzig: Theodor Steinkopff, 1933. Price, Rm. 15.—.

NEW EDITIONS.

Diseases of the Chest and the Principles of Physical Diagnosis. By GEORGE WILLIAM NORRIS, A.B., M.D., formerly Professor of Clinical Medicine, University of Pennsylvania, and Chief of Medical Service "A," Pennsylvania Hospital; and HENRY R. M. LANDIS, A.B., M.D., SC.D., Professor of Clinical Medicine, University of Pennsylvania, and Director of Clinical and Sociological Departments, Henry Phipps Institute of the University of Pennsylvania. With a chapter on The Transmission of Sounds Through the Chest, by CHARLES M. MONTGOMERY, M.D., formerly Physician to the Phipps Institute, Philadelphia; and a chapter on The Electrocardiograph in Heart Disease, by EDWARD B. KRUMBHAAR, PH.D., M.D., Professor of Pathology, University of Pennsylvania School of Medicine. Pp. 997; 478 illustrations. Fifth edition revised. Philadelphia: W. B. Saunders Company, 1933. Price, $10.00.

A Text-book of Medicine. By AMERICAN AUTHORS. Edited by RUSSELL L. CECIL, A.B., M.D., SC.D., Professor of Clinical Medicine, Cornell University Medical College, and Associate Attending Physician, New York Hospital; Associate Editor for *Diseases of the Nervous System;* and FOSTER KENNEDY, M.D., F.R.S.E., Professor of Neurology, Cornell University Medical College, and Director, Department of Neurology, Bellevue Hospital. Pp. 1664; 30 illustrations. Third edition, revised and entirely reset. Philadelphia: W. B. Saunders Company, 1933. Price, $9.00.

A Practical Medical Dictionary. By THOMAS LATHROP STEDMAN, A.M., M.D. Pp. 1256, with many text illustrations; 22 plates, 4 colored. Twelfth revised edition. Baltimore: William Wood & Company, 1933. Price, Plain Edge, $7.00; Thumb Indexed, $7.50.

Since 1908 this book has been quietly exerting its influence for better spelling and use of words. In this edition, about a thousand new words have been added, including a number of terms of the Nomenklatur Kommission (marked N K).

PROGRESS
OF
MEDICAL SCIENCE

ANNOUNCEMENT.

For sometime we have felt the inadequacy of monthly abstracts of isolated articles in attempting to cover the progress of medical science. We have also recognized that this method is being followed by the *Journal of the American Medical Association*, a weekly which is presumably taken by all our subscribers. We have, therefore, decided that, beginning with this number, longer reviews of important topics that have recently undergone considerable development will be presented by two departments each month. The same total space will be utilized as heretofore and each department will be represented twice annually. It is our hope that this plan will furnish our readers with more useful connected and digested information about medical progress than did the method we are abandoning. The recent discontinuance of *Progressive Medicine* makes this change especially timely. We shall be glad to forward to the appropriate Progress Editor any suggestions of desirable topics. [THE EDITORS.]

MEDICINE

UNDER THE CHARGE OF
JOHN H. MUSSER, M.D.,
PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

ANEMIA, DIET AND VITAMIN DEFICIENCY.

THE studies started by Whipple some years ago on the influence of various types of food substances upon the blood picture, and continued in the treatment of pernicious anemia by Minot, who had independently developed the use of large amounts of liver in this condition, have stimulated many in the last few years to study the effect of diet upon anemia in general, and more specifically the effect of diet on the more definite anemia entities. Such studies include those that have to do with the presence of some substance in food which, when lacking, has an influence upon the development of pernicious anemia, upon sprue and the pernicious types of anemia seen in pregnancy or those that have as their etiologic background definite vitamin inadequacy of the diet. Also has been studied idiopathic hypochromic anemia, which, it has been suggested, may depend upon either some deficiency in gastric secretion or on the inability of the gastro-intestinal tract to make use of those food substances which are ingested and which subsequently stimulate blood formation. Many of these studies have appeared in this journal. Only one needs be referred to briefly here. STRAUSS and CASTLE (AM. J. MED. SCI., 1933, **185**, 539) come to the conclusion that the macrocytic anemia of pregnancy may be produced by the lack of the extrinsic factor, vitamin B_2. This type of anemia can be relieved by liver extract, but in some instances supplementary iron rations must also be given. They suggest likewise that the hypochromic anemia of pregnancy is due to a direct dietary deficiency or is

one conditional upon gastric anacidity or associated defects, when the fetal demand for blood-bearing materials has to be met. This may be relieved by iron.

A relatively early communication of CASTLE and STRAUSS (*The Extrinsic [Deficiency] Factor in Pernicious and Related Anemias, Lancet*, 1932, **2**, 111) advanced the hypothesis that there was an extrinsic factor lacking in pernicious anemia and other macrocytic types of anemia, which they believed to be a protein or a closely related substance. Further studies have lead them to believe that vitamin B_2 is the extrinsic factor, or at least a substance closely related to vitamin B_2; furthermore, that these macrocytic types of anemia may be due to a lack of a specific hemopoietic reaction between the extrinsic factor (vitamin B_2) and the intrinsic factor of the normal human gastric juice. In those cases of macrocytic anemia, such as sprue, the disease is due often to a lack of the extrinsic factor. They state, furthermore, that liver extract is rich in vitamin B_2, which may explain the results of feeding liver extracts that occur when the extrinsic factor is lacking in sprue and the anemia is cured by this therapy.

This most fundamental and important work that has been done on the relation of pernicious anemia and related macrocytic anemias to vitamin deficiency has come from the Boston City Hospital under the stimulation of Doctor Minot. CASTLE (*The Etiology of Pernicious Anemia and Related Macrocytic Anemias, Ann. Int. Med.*, 1933, **7**, 2), to whom was awarded, at the Montreal meeting of the American College of Physicians, in February, 1933, the John Phillips Memorial Prize for the best clinical experimental work produced in the year, summarizes in his address succinctly and clearly the explanation of why certain cases of macrocytic anemia will respond to liver extract and to yeast and others only to liver extract. To quote Castle: "The difference appears to depend on the presence or absence of the intrinsic factor. In the light of this evidence it is clear that the common factor for producing macrocytic anemia is the failure of the specific reaction between the extrinsic and the intrinsic factors. These anemias should, then, occur both where, on the one hand, the diet is deficient in vitamin B_2, and on the other hand, where, although the diet is not grossly deficient, lack of the intrinsic factor is found. Thus, sprue and the macrocytic anemias of the tropics occur in communities or in individuals partaking of defective diets and show gastric anacidity less commonly than is found in patients with Addisonian pernicious anemia, who usually have more normal diet habits. In many cases a combination of gastric defect and dietary deficiency may exist, which would have the same result upon the specific hematopoietic reaction as a total absence of either of its components.

"If the evidence be valid that the extrinsic factor or the specific hematopoietic reaction with normal human gastric juice is vitamin B_2, a new concept of the relation of certain vitamins to the conditions caused by their lack would seem to be involved. The action of a vitamin in curing a deficiency may thus be essentially dependent upon a specific process in the gastro-intestinal tract; and the deficiency state not so much a deficiency in the diet as a deficiency of a reaction in the gastro-intestinal tract or elsewhere in the body."

Another aspect of vitamin B deficiency is exemplified by the studies of FOUTS, KEMPF, GREENE and ZERFAS (*Vitamin B Intravenously for*

Treatment of Neurologic Changes in Pernicious Anemia, J. Indiana Med. Assn., 1932, **25**, 448). Their study was instituted because of the many conflicting reports in the literature of the effect of oral liver treatment when central nervous system involvement occurs in pernicious anemia. In this article, a long list is given of those who have had favorable results and an equally long list is given of those who have had unfavorable results in the treatment of the neurologic complications of pernicious anemia. In some instances, even an increase in the neurologic symptoms has been reported to take place in the course of liver therapy. These authors prepared a concentrated extract of vitamin B, containing mainly the B_1 factor and little of the B_2, an extract potent in the curing and relieving of the polyneuritis of pigeons. These patients with pernicious anemia were given the extract for a period varying from 1 to 7 months, without any improvement in their neurologic expressions.

In addition to the studies that have been made on the hemoglobin and red cell content of the blood when the diet lacks vitamin B, SURE and BUCHANAN (*Influence of Deficiency on Differential Leukocyte Count of Albino Rat During Lactation, Proc. Soc. Exp. Biol. and Med.*, 1932, **30**, 174) have studied the leukocyte counts in the presence of a deficiency of this vitamin. There develops a relative lymphopenia and a corresponding polymorphonuclear leukocytosis in the lactating albino rat. A specific effect of vitamin deficiency was implied in that in the majority of the instances there was a great loss of weight associated with inanition.

In a purely clinical paper (*Three Cases of Chronic Dietary Deficiency, Med. Clin. North America*, 1933, **16**, 761), MINOT discusses the symptoms of fatigue, anemia and prolonged coagulation time of the blood which occur when individuals are on a diet that is nutritionally deficient. He insists that successful therapeutic results will be obtained only by a suitable way of living, including the taking of food properly and an optimal diet for the individual patient.

Another phase of the anemias due to nutritional faults is represented by numerous studies that have been made with various types of food substances. In one of these (*A Preliminary Report on the Cure of Nutritional Anemias by One of the Legumes, Am. J. Trop. Med.*, 1933, **13**, 327), COOK and RIVERA studied in Puerto Rico, where the diet of the poor is restricted and monotonous and anemia is common, the potency of the native pea in hemoglobin formation, reviewing notably the work of Hart and Steenbock, who have studied many types of food substances in the control of anemias of a nutritional nature. These observers put rats upon a standard anemia-producing diet. They were then fed a particular pea, the pigeon pea. It was found that these peas exhibited curative properties in the native rat, the fresh peas showing greater regenerative power than did the ash of the equivalent quantities when they were both fed at levels suboptimal to induce normal regeneration. Their experiments demonstrate to the satisfaction of the investigators that there is higher efficiency in blood formation in fresh foods than in inorganic elements.

A very comprehensive study of the nutritional anemias of infancy and early childhood has been presented by PARSONS (*Arch. Dis. Child.*, 1933, **8**, 85). This work is a most thorough clinical and experimental presentation. The paper is divided into several subsections, of which

those germane to the present discussion include a report on the effect of yeast on nutritional anemias in rats. Yeast is rich in vitamin B complex. It contains also iron, both in the organic and inorganic forms, copper and two important caseins, cerevisine and zymocasein. Feeding this yeast to the standard anemic rat, their results were comparable to those who have done similar experiments. The anemia was quickly controlled. In order to do away with the possibility that the copper and iron of the yeast might account for its anemia-relieving properties, a yeast preparation was made with the least possible copper, iron and manganese content. This yeast produced a cure of the anemia, although more slowly than by the other methods, such as the addition of a small amount of iron, which resulted in the formation of more hemoglobin than in the so-called anemic yeast of this author. The next step that was taken, to determine if possible what was the curative factor in yeast, was to give a watery extract of this substance which would contain the vitamin B content and the amino acid salts, but no hematin. Again a cure resulted which was satisfactory. Their experiments allowed them to state that yeast has a curative effect upon the nutritional anemia of rats and allows reproduction to take place. Yeast is more effective when added to a milk diet than copper or iron, judging from the standards based on growth, but it is not a complete supplement. The addition of yeast and iron to milk completely rectifies the diet and overcomes the anemia. They believe that the B complex has a definite influence on hematopoiesis, but that it cannot be regarded as an effective curative agent. The authors are not able to make a categorical response to the questions they have propounded. They do suggest that the results that were achieved are due in part to the iron and copper present in yeast, as well as the vitamin B complex and possibly to amino acids. The clinical studies were carried out on nutritional anemia, the anemias of prematurity, scurvy and celiac disease in a group of infants. Yeast therapy was tried in view of the results that were achieved in the rat experiments. It was found that the yeast was less effectual in the treatment of the nutritional anemias of childhood than in the rat. The anemia of scurvy was very promptly cured by adding orange juice to the diet without any other medication and while the child was on a milk diet. The anemia of celiac disease, from their experiments, was due largely to the absence of Castle's intrinsic factor. The anemia was not relieved by the extract of marmite, which would supply vitamin B complex, although Castle and Rhoads state that in sprue and celiac disease there is at times a lack of the extrinsic factor which can explain the anemia.

Scott and Delor (*Nutritional Anemia, Ohio State Med. J.*, 1933, **29**, 165) fed to the white rat, suffering from nutritional anemia, milk obtained from a Holstein herd fed with warm hydrolyzed alfalfa hay and grain. Another group of animals were fed an iron and copper-free extract of alfalfa and the diet of a third group was augmented by the addition of a liver oil high in vitamin A. They mention the work of Guha, who thinks that both milk and yeast contain a factor that is required for the normal growth of rats which is different from other known vitamins. These experiments, as well as preceding ones, suggest that vitamin A is essential for normal blood regeneration and that vitamin A can cure certain types of nutritional anemias.

Still another paper, based on the work of Steenbock and Hart, is

that of FARMER and CORY (*Hemoglobin Regeneration of Anemic Albino Rat With Dietary Supplements of Spinach, Apricot and Liver, Proc. Soc. Exp. Biol. and Med.*, 1932, **29**, 766), who supplemented the daily rations of rats on the standard anemia diet with spinach, apricot or liver. They noted that the puréed spinach or apricot gave a greater hemoglobin response than did the non-puréed material or the ash. The hemoglobin building ratio of these three foodstuffs is comparable to that achieved in the rats of Robscheit-Robbins which were rendered anemic by bleeding. In their rats, Farmer and Cory found that these food substances, liver, apricot and spinach, can be graded in a ratio of 4–2–1.

BEEBE and WINTROBE (*Effect on Idiopathic Hypochromic Anemia of Beefsteak [Hamburger Steak] Digested With Normal Gastric Juice, Arch. Int. Med.*, 1933, **52**, 464), in discussing idiopathic hypochromic anemia, state that the most generally held opinion is that the anemia depends upon some gastric secretion deficiency or depends upon dysfunction of the absorptive properties of the gastro-intestinal tract. They repeated Castle's original experiments with pernicious anemia patients, beefsteak properly digested with normal gastric juice being fed to their patients with hypochromic anemia. Five individuals were given 200 gm. of beefsteak digested with 100 cc. of normal gastric juice. In no case was there the expected reticulocyte rise, and there was no increase in hemoglobin, in the value of packed red cells and in the red blood count. It would seem to these investigators that in this type of anemia a specific substance is not lacking, and this, despite the fact that in idiopathic hypochromic anemia there occurs an achlorhydria.

An interesting series of papers comes from the Rochester school, as a continuation of Whipple's previous important work. The fifth paper of this new series, by BOGNIARD and WHIPPLE (*The Iron Content of Blood-free Tissues and Viscera, J. Exp. Med.*, 1932, **55**, 653), is interesting because the Rochester investigators find that there is a large reserve store of iron in the liver, spleen and marrow which may be modified by diet. The reserve store of iron may be depleted by an anemia period of 2 to 3 months.

This review is of some of the work only that has been done in the past year in linking up anemia with nutritional faults and dietary inadequacy of vitamin. It is known that anemia may have a different and varied etiology; that dietary errors, be they lack of protein, mineral elements or vitamins, are a very common cause of anemia. Indeed, so frequent are these types of anemia that OTTENBERG (*Reclassification of Anemias, J. Am. Med. Assn.*, 1933, **100**, 1303) suggests an etiologic reclassification of the anemias into three broad divisions: (*a*) The deficiencies, (*b*) direct injury to the blood-making organs, and (*c*) blood destruction from any cause. Fundamentally the anemias due to vitamin deficiency are closely interwoven and definitely related in that one or another of the vitamins is either lacking in the diet or cannot be utilized by the body. Thus, one type of nutritional anemia may develop as a result of inadequacy of vitamin A; the anemia of scurvy can be cured with vitamin C; but, although vitamin B (or B_2) inadequacy has a definite influence on the development of the macrocytic types of anemia, the explanation of the mechanism of production of this type of anemia differs somewhat from the anemias that are produced by deficiency in other vitamins.

PEDIATRICS

UNDER THE CHARGE OF
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POLIOMYELITIS—A SURVEY OF RECENT CONTRIBUTIONS.

In a review prepared more than a year ago (*J. Pediat.*, 1932, **1**, 358) SCHULTZ stated: "Though we may claim to a certain degree of enlightenment as to the cause, nature and effect of poliomyelitis, we are still in the 'thesis stage' of our knowledge of this disease." Since the preparation and presentation of the above paper there have been in different parts of the country outbreaks of this disease, in some localities amounting to severe epidemics. As a consequence much material has been available for the observation and study of the different phases of the disease. Notwithstanding it is a question whether or not the many contributions on the subject have actually contributed any material advance to our knowledge. It would be impossible here to abstract all or even many of these papers, and where some may be abstracted more or less at length, the criterion for dwelling on one presentation rather than another has been the impression made upon the Reviewer rather than the ultimate scientific valuation.

From the standpoint of epidemiology SCHULTZ (*Loc. cit.*) reminds us that it is well established that this disease is spread chiefly, if not entirely, by the dissemination of nasopharyngeal secretions of virus carriers, the virus having been demonstrated in the mucous membranes of the nasopharynx, not only during the acute period of the disease, but also in some cases several months after convalescence. The virus has been demonstrated also in the nasopharyngeal washings of healthy individuals who have been in contact with patients. He also says that the disease may be acquired by means of the milk, but he stipulates that when man acquires the disease by drinking contaminated milk, the infection most likely results from a contact of the virus-contaminated milk with the nasopharyngeal vault, rather than by a passage of the virus from the intestinal tract to the central nervous system by some more or less indirect route. He adds that milk can never act as a culture medium, as in the typhoid-contaminated milk, but merely as a mechanical vehicle of the virus, and it is possible that either foodstuffs might play a similar rôle as a vehicle for the virus from a "virus-carrying food handler" to a new host.

Paralleling this thought we find TOOMEY and AUGUST (*Am. J. Dis. Child.*, 1933, **46**, 262) making a comparison between the epidemic peak and the harvest peak in the neighborhood of Cleveland. They stated that infantile paralysis need not be due necessarily to fruits and the like, but perishable foods might serve as one of the vehicles by which the disease is carried. Such a concept would explain the somewhat explosive and dispersive type of infection that they observed during the harvest peak. They point out that the handling of infected fruit or vegetables, the contamination of fruit and vegetables by infected

persons, the eating of infected fruits and vegetables by cattle with subsequent infection of the milk, and the spreading of the infection from fruit to fruit by flies might explain at least one mode of transmission and the increased incidence at this time of the year.

From the etiologic aspect, it is now recognized that the infection manifests itself in adult life with more frequency than was formerly thought. This has been emphasized by the rise to prominence of our President, Mr. Roosevelt, who suffered his infection in his thirties. Another well-known case is that of Dr. Walter Stewart, of Atlantic City, who reports his case as quoted later. Schultz comments on the experimental attempt of Jungeblut and Engle, in 1931, to show that resistance to to poliomyelitis in adults may be determined by the internal secretions, especially by the glands determining sexual maturity. Schultz questions why the incidence of adult's immunity in a rural district was found by Aycock and Kramer to be less than half the incidence of immune persons in an urban community. This is an argument against the theory of sexual retardation, as there is nothing to indicate that persons living in the country are less well developed than those living in cities. However, it is much more plausible to assume that the immunity results from virus contact, a more likely occurrence in the city than in the country. Immunity may be total, partial or relapsing. Many children and most adults have an acquired if not a natural immunity. In others, there is an incomplete immunity as evidenced by what has been termed, recently, abortive forms of poliomyelitis. To speak of another form of incomplete immunity as relapsing may be a misnomer, as this may be seen in partial immunity with sudden exposure to infection of excessive virulence. The two latter types are well illustrated in the report of Stewart (*J. Pediat.*, 1933, **2**, 393), who for 6 weeks was in contact with 35 various cases of poliomyelitis in the isolation hospital. His first child became infected 7 days before the seizure of the father. It would seem that the father was a carrier for some time prior to the penetration of his own resistance. The first child to become ill passed through a typical illness without the development of paralysis; the second was seized with the prodromal manifestations 2 days after the first. She ultimately developed paralysis of an upper extremity. The third became ill about the same time with an abortive attack. The father became ill 7 days after the first child and developed moderate loss of power of the lower extremities. The mother of the children showed the symptoms of the mild abortive type with no residual paralysis. In this family the father's blood was Group IV (Moss), the mother was Group I and the 3 children were all Group II. This report is of more than ordinary interest as the observations were made by 1 of the patients, who has had the advantage of the best training in pediatrics.

Season may play a part. Toomey and Lipson (*J. Pediat.*, 1932, **1**, 739) studied the influence of season and other factors in the incidence of poliomyelitis. They found that the morbidity curve for this disease showed that the majority of cases occurred during August, September and October in the vicinity of Cleveland. Ordinary factors associated with seasonal changes, such as temperature, dryness, increased precipitation, sunshine and the like did not seem to have any effect upon the case morbidity rate of infantile paralysis. There was a decrease

in precipitation and a normal or increased temperature curve in all but one of the epidemic years.

Regarding blood grouping in poliomyelitis, SHAW, THELANDER and KILGARIFF (*J. Pediat.*, 1932, **1**, 346) present the observation on a group of 100 cases checked with 100 controls. Incidentally it is of interest to compare the results of blood grouping in the Stewart family with the results of this study. It is seen that the higher frequencies are noted in Groups IV and II with few or none in Group I, which was also noted by Grooten and Kassovitch and others. Further study is required on the frequency of incidence and relative severity of the infection in the Moss blood groups. If the findings so far made are borne out in large numbers of cases observed, an aid to diagnosis may be developed as well as a criterion for prognosis. It is conceded universally that early diagnosis is of the utmost importance in permitting early specific treatment. While some question has been raised about the efficacy of serum therapy by some observers, even these for the most part admit that the earlier the therapy is administered the better are the results.

ROSENBERG (*J. Med. Soc. New Jersey*, 1933, **30**, 248) describes the onset of the illness: "The child rapidly becomes feverish and drowsy. In most cases this drowsiness becomes an outstanding symptom. The patient can be aroused easily from this stupor but, when awakened, is strikingly irritable and restless. He particularly does not want to be annoyed, and just as soon as he is left alone relapses into a comatose state. The mind is clear despite this drowsiness, and if the child's coöperation can be engaged, he will complain of two significant symptoms—occipital headache and pain in the back. Starting to examine the patient, the physician may or may not have poliomyelitis in mind, but he will suddenly get the lead as he observes the movements of the child. When he must ask the patient to sit up or turn over, it becomes evident immediately, as the child responds, that there is disinclination to flex the spine, and as the attempt is made to assume the upright position, he extends his arms and rests on his arms placed far behind his back. If the patient should now be asked to fold his arms, he will reluctantly try and quickly revert to his original position. The characteristic posture of supporting himself that the child takes is known as Amoss' sign. If asked to turn over on his abdomen, it will be evident that the movement is painful, and while he is turning it may be noticed that the spine is held straight and stiff as a poker-back." Rosenberg points out that this may be further demonstrated by having the child standing and attempting to touch his toes, without bending his knees. In a true case of poliomyelitis this is impossible. It may be done partially in the early stages of the disease. The back is held rigid and all motion is at the hips. This resistance to anterior flexion is called the "spine sign." The Kernig sign is indeterminate. Other helpful signs and symptoms are enumerated. Stiffness and pain in the back of the neck are early signs. A distinct tremor of the fingers has been noted. This is supposed to be due to irritation of the anterior horns before degeneration has developed. Hyperesthesia is another early and prominent symptom. Tenderness along the spine and down the legs may be present. Muscular pain and twitchings are commonly located in one or more groups of muscles. There is an excessive response

to the patellar reflex early. Gastro-intestinal symptoms are usually seen early in the disease. They may be so marked as to give the impression that this is the only cause for the temperature. Sweating is very common, especially in the severer cases. The eyes show significant changes, such as glazing of the sclera and cornea, and there is circumorbital puffiness. In other infectious diseases the eyes are bright and shiny. The pre-paralytic stage lasts in most cases for 4 days. If there is no paralysis by the 8th day there is little danger of its occurrence. Diagnosis in this stage may be difficult, because all cases do not run the typical course. Rosenberg points out that the most valuable symptoms in the pre-paralytic stage are those referable to the spine: occipital headache, poker-back attitude, resistance to motion of the spine and hyperesthesia of this region. Diagnosis is usually cleared by spinal fluid examination. GONCE (*Journal-Lancet*, 1932, **52**, 548) says that the spinal fluid pressure may or may not be increased. The fluid may be clear, where the cell count is still low, or hazy, or have a ground-glass appearance in the presence of a high concentration of cells. The number of cells averages from 200 to 300, but the variation may be as great as from 20 to 1200 or more. The examination of the cells should be made within an hour as the cells tend to disintegrate. Albumin and globulin are moderately increased. The sugar may be normal or slightly increased. In the presence of epidemic, the diagnosis is usually made in even the atypical and mild forms. In sporadic cases it is easily possible to err if the case is not typical in its clinical picture.

A recent interesting study of the pathway of invasion as determined by the localization of the virus during the pre-paralytic stage was made by FABER (*Am. J. Dis. Child.*, 1933, **46**, 680): "With an improved technique for intranasal inoculation of monkeys with poliomyelitis virus, the pathways followed by the virus from the nasal mucous membrane into and through the central nervous system and the approximate rate of invasion were determined. It was found that about four days were required for the virus to appear in detectable amounts in the central nervous system and then only in the olfactory bulb. By the fifth day it had spread to the hypothalamus and medulla, but it was not found elsewhere. On the sixth day it was present in the olfactory bulb, hypothalamus, midbrain and medulla, but not elsewhere in the brain or spinal cord. On the seventh day it was found for the first time in the spinal cord and spinal ganglions. This rather slow spread by continuity from a definite and sharply localized initial focus through the brain stem to the cord, with the avoidance of contiguous structures in the end brain and cerebellum, shows that the propagation of infection in poliomyelitis is not through the blood or the cerebrospinal fluid, but through the axons of the nerves, as previously demonstrated by Fairbrother and Hurst. As the inoculations correspond with the natural portal of entry in man, the inference is made that the route of invasion found in monkeys corresponds with that in man. If this conclusion is correct, the concept of the human disease as consisting of a preliminary stage of systemic, extranervous infection followed by invasion of the central nervous system through a hypothetically damaged 'meningochoroid barrier' is no longer tenable. The origin of some of the characteristic symptoms at the onset of poliomyelitis in man can, it is

believed, be traced to certain areas in the hypothalamus, thalamus and elsewhere in the brain stem which the virus traverses and infects, at least transiently, during its passage toward the spinal cord. A tentative classification of symptoms in chronologic order of development is offered, the clinical disease being divided into four successive phases: (1) The cerebral or diencephalic phase; (2) the phase of posterior poliomyelitis; (3) the phase of anterior poliomyelitis; (4) the phase of recovery. The advance of the disease may cease at the end of Phase 1 or Phase 2, giving rise to the so-called abortive type of poliomyelitis."

During the epidemics we are confronted by the demand of parents to undertake measures to prevent their children from developing the disease. A great many measures were taken during the late epidemic, and many children were injected with different materials. CARPENTER, STOKES and WOLMAN (*Am. J. Dis. Child.*, 1933, **46**, 681), in a paper dealing with their experiences in immunizing against poliomyelitis, state: "During the epidemic of poliomyelitis in Philadelphia in the summer of 1932, an effort was made for widespread prophylaxis against the disease by passive immunization. So far as we are aware, such a procedure on a large scale has not been attempted previously. Six hundred and twenty children, under 10 years of age, residing in a carefully investigated census area where the disease incidence was highest, were given intramuscular injections of 66 cc. of parent's whole blood at the Children's Hospital of Philadelphia. Three mild cases of poliomyelitis without paralysis appeared in this group, an incidence of 1 in 207, whereas, according to the statistics of the Bureau of Health, the incidence of the remaining children in the same area in the same age group during that period was 1 in 640." In 721 children living outside the census area getting similar injections, 3 mild cases developed. Of 838 other children receiving blood or serum in various amounts, so far as we can determine, none subsequently had poliomyelitis. "The ages ranged from 1 to 15 years, although the large majority were under 11 years. The incidence in this entire number of 2179 children was 6 cases, or 1 in 363. In the city as a whole, of an estimated population of 289,500 children under 11 years of age, 521 cases of poliomyelitis occurred, an incidence of 1 in 555." From an undetermined number of prophylactic injections of various kinds variously given, data were collected on 11 children, who developed the disease. "In 1 child, severe paralysis of both legs developed, in another, moderate paralysis of one extremity, and in 2 others, slight transient weakness of one extremity. The remainder had no paralysis or weakness, and there were no deaths. Considered as a group, these children had a favorable course as compared with the rest of the children with this disease in the city, for of the 687 cases in Philadelphia, paralysis developed in about 70 per cent, and the mortality rate was 11.5 per cent. The blood of the donor for the child who was paralyzed in both legs was found to fail to neutralize a 5 per cent suspension of Philadelphia virus. The other child who was paralyzed received but 8 cc. of pooled convalescent serum. Although the series of cases is small, we believe that the data suggest that passive immunization by means

of adult or convalescent blood or serum is of value as a prophylactic measure against anterior poliomyelitis."

There exists a difference in opinion as regards the value of the active treatment of this disease by serum therapy. It is agreed, however, that serum therapy, if effective at all, must be administered early in the illness. PARK (*New York State J. Med.*, 1933, **33**, 91) states that it is now definitely known that poliomyelitis is due to a filterable virus. He feels that this is of great importance, as there is no other disease due to a filterable virus that can be benefitted by an antiserum after clinical symptoms have developed. He refers to the studies made by Kraemer and Aycock during the 1931 epidemic, where, in better controlled experiments than any previously made, there was no statistical evidence that convalescent serum was effective. However, the opposite conclusion, that it was of no value, could not be drawn. In order to test the comparative value of the different methods of giving the serum, Park administered it to some of the patients by the Aycock method of combined intraspinal and intravenous injections, and by the Canadian method of subcutaneous injections. He also treated a number of patients by the intravenous method alone or combined it with the intramuscular injection. He varied the total dose from a minimum of 25 cc. to a maximum of 100 cc. Those persons treated in the first day of their meningeal symptoms showed somewhat better results than those treated later in the illness. However, in some cases even those treated later showed surprisingly good results, and on the other hand there were some good results in the untreated patients. It was observed that the route made no appreciable difference in the outcome. Those who received it intramuscularly developed in a larger percentage of cases some weakness, yet this was of very mild form. There seemed to be little or no statistical evidence of any difference between the serum treated and the untreated patients with pre-paralytic poliomyelitis based upon the studies of the Poliomyelitis Committee of the Academy of Medicine of New York City. The slight difference in favor of the untreated patients probably may be attributed to the accidental inclusion of a somewhat larger number of graver cases in the treated group. Park points out that statistically there was no evidence that the serum did any good, nor was there any evidence that it did any harm. The results of these controlled investigations indicate that in epidemics only a portion of the cases should be treated with serum, and the untreated cases should be observed with equal care, so that finally a conclusion may be reached as to whether the serum has any value at a time when the spinal cord is already invaded by the virus of poliomyelitis.

This viewpoint regarding serum therapy of poliomyelitis has been taken by a number of recent authors. WESSELHOEFT (*J. Pediat.*, 1933, **3**, 330), SMELIE (*Arch. Dis. Child.*, 1933, **8**, 75) and PETTE (*Deutsch. med. Wchnschr.*, 1933, **59**, 873) are a few of those who agree with Park and Aycock and Kraemer. SHERMAN (*Deutsch. med. Wchnschr.*, 1933, **59**, 1332) gives us the results of a variation of the methods of serum therapy. He reports treating 55 patients having acute anterior poliomyelitis by means of convalescent serum. He used the intraspinal and the intramuscular methods with doses of from 50 to 100 cc. Not get-

ting satisfactory results, he began transfusion of blood from convalescent patients. He based this change upon the fact that the blood is fresh and unchanged, and that it could be given in larger quantities than the serum, and because there is a possibility that the protective power of the whole blood is greater than that of the serum. This treatment was given to 71 cases (from 150 to 400 cc.). The transfusions were found to give much better results than the serum therapy. Not only were the mortality rate and the frequency of paralysis lowered, but on the course of the fever and on the general symptoms of the acute infection were lessened. He advises that records be kept of suitable donors for use in subsequent outbreak.

The cases that develop paralysis comprise what may be called the chronic group. In the slight cases prolonged rest, massage and modified electrical treatments may result in a more or less complete restoration of function. Basically, however, the slight, as well as the severe, forms become orthopedic problems. Many contributions to the literature of this phase of the disease are found. WHITMAN (*New York State J. Med.*, 1931, **31**, 1397), TODD (*Lancet*, 1932, **223**, 1044) and RYERSON (*J. Am. Med. Assn.*, 1933, **101**, 1376) are a few contributors to the problems of the chronic stage. BOORSTEIN (*Med. J. and Rec.*, 1932, **135**, 27) is cited because of his recommendations for the orthopedic treatment during the acute and convalescent stages. RUHRAH (*J. Pediat.*, 1933, **3**, 217) gives the treatment of poliomyelitis both past and present. In his paper he deals with the history of the disease, but in concluding his presentation he summarizes the chief points. While his summary is rather general in character, it so well epitomizes the postparalytic care that it is quoted in full: "(1) The tendency is to recovery, much of the permanent paralysis is due to neglect or improper management. (2) Contractions and deformity can be avoided. (3) The principal thing in the treatment is rest, with the body recumbent, but in the position it would be in if standing erect. (4) The most important muscles should be favored early and until their recovery is assured. (5) Special adjustments of splinting must be made to favor muscles which should have it. (6) Fatigue, general and local, should be avoided. (7) Weight-bearing should not be allowed as long as recovery is expected. (8) Especial care should be taken not to allow at any time any stretching of affected muscles. (9) When recuperation is well established, carefully supervised exercise within the capacity of the muscle is of value. (10) Warm salt baths, very gentle massage (only after all tenderness has disappeared), fresh air and sunlight and warmth are valuable adjuvants in the treatment. (11) The splints or braces should be inspected frequently and changed to suit conditions. (12) The transition to weight-bearing should be gradual, avoiding overexertion and fatigue. (13) After all the improvement has been obtained that can be looked for as judged by a failure to improve under proper management, the patient should be gotten on his feet, using such apparatus as may be necessary. Old and neglected cases will need orthopedic care to correct deformity and exercise to develop latent muscle power. (14) Every case should be treated individually and not by any fixed routine. Changes should be made to suit conditions as they arise and deformities due to lack of balance of muscles carefully avoided."

PHYSIOLOGY

PROCEEDINGS OF

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Zinc Hydroxid Powder as a Precipitant in a Simplified Procedure for the Preparation of Protein-free Filtrate of Blood.—T. V. Letonoff (Laboratory of the Division of Metabolism of the Philadelphia General Hospital). In connection with work on a method for the micro determination of chlorid in blood and plasma, it was necessary to employ a simple protein precipitant that would remove purins and yield a neutral filtrate. Various available procedures for removal of proteins were tested, but none were found satisfactory. In trying various substances, powdered zinc hydroxid was found to remove protein from diluted blood.

Trial of this substance indicated that it possessed many advantages that recommended its more general application in place of other protein precipitants. It was found that the use of powdered zinc hydroxid offered all of the advantages of the Somogyi procedure, yet eliminated the need for standardized solutions of sodium hydroxid and zinc sulphate. Only traces of zinc appeared in the filtrate. In most methods of precipitating proteins, considerable quantities of the reagents are present in the filtrate. Saccharids were removed completely, so that the level of true fermentable sugar could be determined directly by alkaline copper reagents. The filtrates are neutral and may be used also for urea nitrogen, non-protein nitrogen, creatinin, and creatin determinations. It is believed that this procedure may have useful application in biologic chemistry.

Studies on the Mechanism of Sulphur Oxidation.—James C. Andrews and Kathleen C. Andrews (Laboratory of Physiological Chemistry, University of Pennsylvania). Although it is commonly assumed that the metabolic oxidation of cystin to inorganic sulphate involves the formation of a sulphonic acid such as cysteic acid, the great stability of this latter compound makes it difficult to explain its decomposition to give inorganic sulphate. It has been found impossible to obtain sulphate from cysteic acid under any conditions resembling those *in vivo*, and its administration to animals by other investigators has not caused increased excretion of inorganic sulphate.

The authors have investigated properties of certain cyclic sulphonic acid derivatives of cystin, such as cysteic acid hydantoin and cysteic acid phenyl hydantoin. These compounds are very unstable, and on neutralization with dilute alkali at ordinary temperatures they yield inorganic sulphate directly. The phenyl derivative yields about 15 per cent of its sulphur as inorganic sulphate, the simple hydantoin about 10 per cent. Other evidence points to two simultaneous methods of decomposition, one involving loss of H_2SO_4 and the other involving a split in the hydantoin ring, producing an open chain compound, the sulphur of which remains stable as the sulphonic acid.

A further study of the mode of decomposition of these and similar cyclic sulphur compounds is planned by the authors.

Relation of Nerve Regeneration to Contractility of Arterioles in the Rabbit's Ear.—E. R. Clark, E. L. Clark and R. G. Williams (Laboratory of Anatomy, University of Pennsylvania). In the new tissue which grows in the space left in the "round table" chambers inserted in the rabbit's ear, there occurs a growth and differentiation of definite arterioles, capillaries and venules, the exact ages of which may be recorded photographically. Some of the arterioles develop a very definite power of contraction and dilatation, while others do not develop active contractility. There may also occur a growth into the chamber of a variable number of nerves. These, if non-myelinated, can rarely be seen without the use of vital staining. However, by an adaptation of the use of methylene blue, temporary staining of the axones has enabled us to see the non-myelinated nerves.

By combining the two methods, namely, by watching and recording the extent of definite contractions, and subsequently staining and recording the nerves, we have succeeded in demonstrating, on three successive stages in the same animal, at 10- and 9-day intervals, the progressive and coëxtensive side-by-side development of definite contractility in a newly forming arteriole, and of newly formed non-myelinated nerves; there were no nerves along arterioles which failed to show contractility. The contractions of the artery are considered to be the result of impulses reaching them through the nerves, since they occurred simultaneously with contractions of the original arteries of the ear whose nerve supply was undisturbed, contractions which could be brought about with ease by startling the rabbit either by a noise or some mechanical disturbance, while other arterioles along with all capillaries and venules showed slowing of blood flow, but no appreciable change in caliber.

The ages of the successive portions of the arteriole at the time of the inauguration of active contractility varied between 8 and 26 days. Ages of arterioles at the commencement of contractility in the other chambers have varied from 9 days to $7\frac{1}{2}$ months.

The rate of growth of the nerves and of the extension of contractility in the arteriole dropped from an average of 70 micra per day during the first 10-day period to an average of 28 micra per day during the succeeding 9 days.

These observations prove that the nerves which control the contraction of muscle cells on arterioles may undergo new growth at the periphery in the adult animal, and may establish nerve control over vessel contraction.

The Nature of the Osmotic Effect of Solutions of Non-electrolytes on the Erythrocyte.—M. H. Jacobs (Laboratory of Physiology, University of Pennsylvania). It has been known for many years that the erythrocyte swells less and is less easily hemolyzed in hypotonic solutions of non-electrolytes than in those of electrolytes of the same osmotic pressure. The most generally accepted explanation of this apparent anomaly is that in non-electrolyte solutions the internal osmotic pressure of the cell is more easily lowered by a loss of salts to the surrounding medium. Experiments by the hemolysis method, carried out with the assistance of Dr. A. K. Parpart, indicate that while an escape of salts from the erythrocytes of the ox into a surrounding sucrose solution

undoubtedly occurs in experiments of sufficiently long duration, this change is much less striking than an earlier one of a different nature, which begins almost instantly and is practically complete within a few minutes. The initial change, which unlike the later one is readily reversible, is believed to be due to an exchange of anions from the cell for hydroxyl ions from the solution, the resulting increase in the base bound by hemoglobin causing a decrease in the osmotic pressure of the cell contents. Calculations indicate that the expected osmotic effect of such an ionic shift is of the order of magnitude of that actually observed.

Effect of Adrenalectomy on Salt Metabolism in Rats.—MITCHELL I. RUBIN and ELIZABETH T. KRICK (Laboratory of Department of Pediatrics, University of Pennsylvania; Children's Hospital of Philadelphia). Studies on the salt metabolism following a complete bilateral adrenalectomy in white rats were presented.

Balance studies of calcium, magnesium, sodium, potassium, phosphorus, chlorin and nitrogen were made before and after adrenalectomy. It was found that during adrenal insufficiency there was a marked loss from the body of all elements studied, so that in most instances a negative balance resulted.

A salt mixture solution containing a combination of the chlorids of calcium, magnesium, sodium and potassium was used to treat these animals during adrenal insufficiency. It was found that the signs of adrenal insufficiency could be made to disappear when such a fluid mixture was substituted for the distilled water used in the control periods. The authors feel, however, that the salt mixture used is not adequate, since some animals while on this mixture died spontaneously of insufficiency after two or three months.

A comparison of results was made between the use of the salt mixture and normal saline as treatment fluid.

The studies presented suggest that the adrenal gland probably regulates, in some way, the metabolism of the salts and the water of the body.

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